CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212194Orig1s000

OTHER REVIEW(S)

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2019184
NDA Number/Referenced IND for NDA:	NDA 212194/IND 126094
Applicant:	Alnylam Pharmaceuticals
Established Name/Trade Name:	Givosiran (Givlaari) 2.5 mg/kg once monthly subcutaneous injection
Indication:	As a monotherapy for the treatment of acute hepatic porphyria in adults (b) (4)
Meeting Type/Deliverable:	Review
Review Division:	Division of Hematology Products (DHP)
Clinical Reviewer	Andy Dmytrijuk
Clinical Team Leader (TL)	Robie Suh
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COA Reviewer:	Yasmin Choudhry
COA TL:	Selena Daniels
COA Associate Director:	Elektra Papadopoulos
Date Consult Request Received:	May 28, 2019
Date COA Review Completed:	October 29, 2019

Please check all that apply: ☒Rare Disease/Orphan Designation

(b) (4)

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to NDA 212194 for givosiran. The Applicant is under NDA review of their drug development program. The proposed indication is treatment of acute hepatic porphyria (AHP) in adults (b) (4) .

The Applicant utilized the following patient-reported outcome (PRO) assessments in their randomized, double-blind, placebo-controlled multicenter, phase 3 clinical trial (Study ALN-ASI-003; hereon referred to as ENVISION) in adult patients with AHP (Table 1):

Table 1. COAs Included in Study ENVISION

COA Name (COA Type)	Concept(s)	Endpoint Position[1]	Copy of COA
Brief Pain Inventory-Short Form (BPI-SF) Item 3 (PRO)	Pain intensity	Secondary	Appendix A
Brief Fatigue Inventory-Short Form (BFI-SF) Item 3 (PRO)	Fatigue severity	Secondary	Section 5.1 Patient Symptom and

[1]Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.

COA Name (COA Type)	Concept(s)	Endpoint Position[1]	Copy of COA
			Experience Report (SDN 9[2])
Nausea Numeric Rating Scale (Nausea NRS) (PRO)	Nausea severity	Secondary	Section 5.1 of Patient Symptom and Experience Report (SDN 9[2])
12-item Short-Form Health Survey (SF-12) Physical Component Summary (PCS) (PRO)	AHP impacts (general health, role limitations, bodily pain, and physical functioning)	Secondary	Appendix B
Patient Global Impression of Change (PGIC) (PRO)	Overall health status	Exploratory	Appendix C

PRO= Patient-reported outcome

This review focused on the PRO assessments (b) (4) (i.e., BPI-SF Item 3, SF-12 PCS, and PGIC). (b) (4).

This submission included a Patient Symptom and Experience Report, which was semi-equivalent to a PRO evidence dossier. The Division seeks COA Staff input on the adequacy of the PRO instruments (b) (4).

The review concludes that there are some potential measurement challenges with the PRO instruments that might affect data interpretability. Below are some specific comments related to each instrument.

- BPI-SF Item 3
  - While the BFI-SF does not specifically measure neuropathic pain, pain in general does appear to be clinically relevant and meaningful to patients[3].
  - Although the BPI-SF Item 3 appears fit-for-purpose[4] for the context of this drug development program, the Applicant was not able to demonstrate treatment effect on pain (i.e., statistically significant reduction in pain).
  - The sponsor's proposed endpoint uses the area under the curve (AUC) approach[5] which is not interpretable, as it is a weighted sum of weekly change from baseline.
  - Minimal reductions in pain were observed in both treatment arms when examining data in a mean change from baseline analysis (non-AUC approach) and it is unknown whether these are meaningful reductions.

[2]Section 5.3.51 of the electronic common technical document in patient-reported outcomes folder under ENVISION folder.
[3]The Voice of the Patient Report of an Externally-Led Patient-Focused Drug Development Meeting Acute Porphyrias, April 1, 2017; https://www.fda.gov/media/130386/download
[4]Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; https://www.ncbi.nlm.nih.gov/books/NBK338448/)
[5]The AUC over 6 months in the respective score will be calculated for each patient, and the mean AUC will be compared between treatment arms in an ANCOVA model.

- The Division of Hematology Products and Office of Biostatistics may want to consider exploration of the BPI-SF Item 3 data to determine whether a meaningful effect of the treatment on pain was achieved.

- SF-12 PCS
  - While the SF-12 PCS demonstrated statistical significance, this endpoint was viewed as an exploratory since the higher ranked BPI-SF Item 3 endpoint failed in the hierarchy of tests.
  - The data from this domain are difficult to interpret due to the following:
    - PCS score included concepts that may not be content relevant for the target population (general health, moderate activities, climbing stairs) based on cited qualitative data in the Patient Symptom and Experience report.
    - A few number of items (single bodily pain item, 1 item from the Role Physical domain, 1 item from General Health) contributed more to the total PCS score. Further there is minimal change in these items based on the descriptive statistics.

- PGIC
  - The concept of interest was related to overall health status and not specific to AHP.

(b) (4)

For future clinical trials in this indication, we recommend sponsors to obtain patient input to ensure that the most important clinical outcomes are measured, as well as to inform endpoint selection and hierarchy. Disease understanding is critical to COA selection and development. As such, there should be a clear understanding of the natural history of the disease including what are the core symptoms that may improve from treatment, disease symptom trajectory (acute, chronic), and the appropriate time course to see a clinical benefit. The endpoint should clearly reflect the outcome of interest (e.g., acute symptoms, chronic symptoms) and the data should be able to be communicated in a way that is accurate, interpretable, and not misleading. Particularly, with this condition it will be important that the selected endpoints are reflecting different aspects of the patient experience and not the same experience (e.g., porphyria attacks cause a host of symptoms that may be alleviated once the attacks are treated).

We recommend sponsors to engage FDA early (e.g., Pre-IND) and throughout drug development to discuss COA endpoint strategy to ensure the selected instruments are fit-for-purpose and are well-defined and reliable for the context of use prior to initiation of pivotal studies.

B. CLINICAL OUTCOME ASSESSMENT REVIEW

1 BACKGROUND AND MATERIALS REVIEWED

Regulatory Background:

Givosiran is not approved in any territory. Orphan drug (OD) designations were granted on 29 August 2016 by EMA (EU/3/16/1731) and FDA (Reference identification number [Ref. ID] 165355) for the treatment of AHP. The FDA granted a Breakthrough Therapy Designation for givosiran on 23 May 2017 (Ref. ID 4101981) for the prophylaxis of attacks in patients with AHP.

Previous COA Reviews:

- C2019077_NDA 212194_Choudhry dated April 29, 2019 (DARRTS Reference ID: 4424490)

Disease Background:

The acute hepatic porphyrias (AHPs) are a family of rare, serious and life-threatening metabolic disorders predominantly caused by a genetic mutation in 1 of the 8 enzymes responsible for heme synthesis. The AHPs include Acute Intermittent Porphyria (AIP), Hereditary Coproporphyria (HCP), Variegate Porphyria (VP), or ALA dehydratase deficient porphyria (ADP); AIP is the most common AHP type. All AHP are due to autosomal dominant loss-of function mutations in enzymes in the heme biosynthetic pathway, with the exception of ADP, which is the result of autosomal recessive mutations.

Acute attacks are triggered by stress factors that induce the expression of aminolevulinic acid synthase 1 (ALAS1), which is the rate limiting step in heme synthesis. Disease symptom onset in AHP patients typically occurs after puberty, with women (~80%) more commonly affected than men. Patients experiencing acute attacks present with highly morbid and potentially life-threatening symptoms that relate to widespread dysfunction across the central, peripheral, and autonomic nervous system. The most debilitating and frequent symptom during acute attacks is diffuse, severe neurovisceral pain, most often in the abdomen, back, or limbs. Other common attack signs and symptoms include nausea and vomiting, fatigue, hypertension, tachycardia, motor weakness, hyponatremia, and mental status changes.

Investigational Product:

Givosiran is a synthetic chemically modified small interfering RNA (siRNA) targeting ALAS1 mRNA and bearing a triantennary N-acetyl galactosamine ligand conjugated to the sense strand. Patients randomized to receive givosiran will be administered 2.5 mg/kg SC monthly during the 6-month treatment period; patients will receive 1.25 mg/kg or 2.5 mg/kg SC monthly during the open-label extension period.

Other materials reviewed:

- Submission (SDN 9) (Patient Symptom and Experience Report)
- DHP consult request dated May 28, 2019
- Previous COA Review: C2017-252 IND 126094 Campbell dated August 28, 2017 [Reference ID: 4145969]

2 FIT-FOR-PURPOSE SUMMARY

Table 2 summarizes the fit-for-purpose assessment for the context of this drug development program.

Table 2. Fit-for-purpose assessment (based on available evidence)

COA Name(s)	Attribute sufficiently established[6]	Supported by:	Location of Supporting Materials
Brief Pain Inventory-Short Form (BPI-SF) Item 3	☒ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☐ No	☒ COA concept is clear and is able to be linked to a clinical benefit attributable to the drug ☒ Face validity (concepts/items appear relevant and no important concepts are missing, e.g., based on discussion with clinical reviewer, clinician input ☒ Evidence of content validity (e.g., qualitative research) ☐ COA is sensitive to detect change ☐ COA is culturally adapted and adequately translated, if appropriate ☒ Other (see Reviewer's comments)	See Section 6.3.1.1 of Appendix 3 of Patient Symptom and Experience Report (SDN 9[7])
12-item Short-Form Health Survey (SF-12) Physical Component Summary (PCS)	☐ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☒ No	☐ COA concept is clear and is able to be linked to a clinical benefit attributable to the drug ☐ Face validity (concepts/items appear relevant and no important concepts are missing, e.g., based on discussion with clinical reviewer, clinician input ☐ Evidence of content validity (e.g., qualitative research) ☐ COA is sensitive to detect change ☐ COA is culturally adapted and adequately translated, if appropriate ☒ Other (see Reviewer's comments)	Not applicable
Patient Global Impression of Change (PGIC)	☐ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☒ No	☐ COA concept is clear and is able to be linked to a clinical benefit attributable to the drug ☐ Face validity (concepts/items appear relevant and no important concepts are missing, e.g., based on discussion with clinical reviewer, clinician input ☐ Evidence of content validity (e.g., qualitative research) ☐ COA is sensitive to detect change ☐ COA is culturally adapted and adequately translated, if appropriate ☒ Other (see Reviewer's comments)	Not applicable

[6] See Sections 5, 6, and 7 of this COA review for more detailed information.
[7] Section 5.3.51 of the electronic common technical document in patient-reported outcomes folder under ENVISION folder.

Reviewer's comment(s): *Although the BPI-SF Item 3 appears fit-for-purpose for the context of this drug development program, the Applicant was not able to demonstrate treatment effect on pain (i.e., statistically significant reduction in pain).*

While the SF-12 PCS has been accepted in other therapeutic areas, the concepts included in the PCS score does not appear to be content relevant for this target population based on cited qualitative data in the Patient Symptom and Experience report. See Section B(7) of this review for more details.

The PGIC measures overall health status and is not specific to AHP. See Section B(3.4) of this review for additional comments regarding the limitations of this instrument.

3 CONTEXT OF USE

3.1 Clinical Trial Population

The target population for Study ENVISION includes adolescents (≥12 years) and adults (≥18 years) with a documented diagnosis of AHP HCP, VP, or ADP based on clinical features (e.g., acute attacks of abdominal, back, chest, extremities, and/or limb pain).

A complete list of the inclusion and exclusion criteria is summarized in the clinical study protocol ALN-AS1-003.

Reviewer's comment(s): (b) (4) . *Note that there was not an inclusion criterion for subjects to have a certain threshold of pain intensity at baseline. Based on the clinical study report, about half of patients had chronic symptoms when not having attacks.*

3.2 Clinical Trial Design

Table 3 describes the clinical trial design of Study ENVISION.

Table 3. Clinical Trial Design for Study ALN-ASI-003

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	☐ Single arm ☒ Open label extension ☒ Double-blind ☒ Randomized ☒ Placebo-/Vehicle-controlled ☐ Active comparator-controlled ☐ Cross-over ☒ Multinational	~ 38 months[8]	Yes

[8] Includes up to 2 months of screening, up to 35 months of treatment (6-month treatment period (double-blind) + up to a 29-month open-label extension period), and a 1-month follow-up period.

Trial Phase	Trial Design	Trial Duration	Registration Intent
	☐ Non-inferiority		

Refer to the clinical study protocol ALN-AS1-003 for more details on the clinical trial design.

3.3 Endpoint Position, Definition, and Assessment Schedule

Table 4 describes the intended placement of the COA in the endpoint hierarchy, including the endpoint definition and assessment schedule for Study ALN-ASI-003.

Table 4. Endpoint Position, Definition, and Assessment Schedule for Study ALN-ASI-003

Endpoint Position	Assessment (If COA, specify Name and Type)	Endpoint Definition	Assessment Frequency
Primary	Electronic diary (eDiary)[9] (PRO/ObsRO)	Annualized rate of porphyria attacks[10] over 6-month double-blind period	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: At 6 months** ☐ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	BPI-SF Item 3 (PRO)	Comparison of mean AUC[11] (over 6 months) between treatment arms	☒ **Daily** ☐ Weekly ☐ Monthly ☐ Other: ☐ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	Nausea 11-point numeric rating scale (PRO)	Comparison of mean AUC[10] (over 6 months) between treatment arms	☒ **Daily** ☐ Weekly ☐ Monthly ☐ Other ☐ Assessment at cross-over or early discontinuation

[9] In instances when the eDiary is not used to report potential porphyria attacks, study centers may be notified by telephone by patients, caregivers, or other healthcare providers.
[10] Attacks requiring hospitalizations, urgent healthcare visit, or IV hemin administration at home
[11] The AUC over 6 months in the respective score will be calculated for each patient, and the mean AUC will be compared between treatment arms in an ANCOVA model.

Endpoint Position	Assessment (If COA, specify Name and Type)	Endpoint Definition	Assessment Frequency
Secondary ☒ Multiplicity adjusted	Brief Fatigue Inventory-Short Form Item 3	Comparison of mean AUC[10] (over 6 months) between treatment arms	☒ **Daily** ☐ Weekly ☐ Monthly ☐ Other: ☐ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	SF-12 PCS	Change from baseline in SF-12 PCS at 6 months	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: Screening, Month 3, and Month 6** ☐ Assessment at cross-over or early discontinuation
Exploratory ☐ Multiplicity adjusted	PGIC	Descriptive statistics	☐ Daily ☐ Weekly ☐ Monthly ☒ **Other: Months 6 and 12** ☐ Assessment at cross-over or early discontinuation

ObsRO= Observer-reported outcome; **PRO=** Patient-reported outcome

Reviewer's comment(s): *The BPI-SF Item 3 was completed (as part of a daily diary via an electronic hand-held device (Samsung E5 Smartphone). The SF-12 and PGI-C were collected by paper.*

(b) (4)

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4 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the COAs are summarized in Table 5.

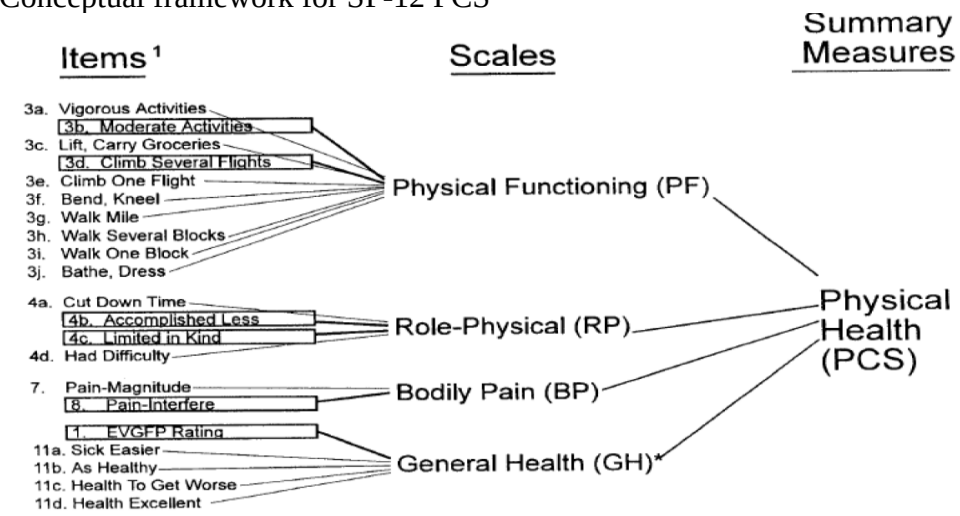
Table 5. Concept of Interest for COAs Included in Study ALN-ASI-003

COA name	Concept(s)
BPI-SF Item 3	Worst Pain intensity
SF-12 PCS	AHP Impacts

Reviewer's comment(s): *Pain (abdominal, back, extremities) appears to be a relevant symptom in patients with AHP (See Section B(7) of this review). Of note, the BPI-SF Item 3 does not specify the location of pain, however based on qualitative data and discussion with Clinical this is not a critical issue.*

The conceptual framework for BPI-SF Item 3 is reflected in Table 4 since it is a single item. The conceptual framework for SF-12 PCS is shown in Figure 1.

Figure 1. Conceptual framework for SF-12 PCS[12]



5 CLINICAL OUTCOME ASSESSMENT(S)

Brief Pain Inventory-Short Form (BPI-SF) Item 3
The BPI-SF Item 3 is a single-item from the BPI-SF, which is designed to assess worst pain intensity on an 11-point numeric rating scale (0=No pain to 10=Pain as bad as you can imagine). The recall period is "in the last 24 hours." A copy of the instrument is in Appendix A.

12-item Short Form Health Survey (SF-12) Physical Component Summary (PCS)
The SF-12 is a generic measure of health status which includes 12 items under the following 4 subdomains. The SF-12 is a 12-item PRO instrument designed to assess generic health outcomes (including the impact of any and all illnesses on a broad range of functional domains). It consists of eight domains:

- General Health, which includes 2 items rated on a 5-point verbal rating scale (ranging from "Excellent" to "Poor*"*); recall period is unspecified.
- Physical Functioning, which includes 2 items rated on a 3-point verbal rating scale ("Yes, limited a lot"/ "Yes, limited a little"/ "No, not limited at all"); recall period is 4 weeks.
- Role Physical, which includes 2 items rated on a 5-point verbal rating scale (ranging from *"All of the time" to "None of the time"*); recall period is 4 weeks.
- Bodily Pain, which includes 1 item rated on a 5-point verbal rating scale (ranging from "All of the time" to "None of the time"); recall period is 4 weeks.

A copy of the instrument is in Appendix B.

Patient Global Impression of Change (PGIC):
The PGIC is a single-item PRO instrument designed to assess change in "overall status" on a 7-point verbal rating scale (1= Very much improved to 7=Very much worse). The recall period

[12]John E Ware Research Group, SF-12: How to score the SF-12 Physical and Mental Health Summary Scales: https://www.researchgate net/publication/242636950

requires the patient to compare their current state with an earlier period ("since the start of the study"). AS copy of the instrument is in Appendix C.

Reviewer's comment(s): *This particular scale is susceptible to recall error and lacks the ability to allow change from baseline analyses.*

6 SCORING ALGORITHM

BPI Item 3

Scores range from 0 to 10, with higher scores representing greater pain intensity.

Reviewer's comment(s): *In this study, the daily worst scores for pain were averaged into a weekly (i.e., 7 day) score. The change from baseline in weekly mean scores was defined as the postbaseline weekly mean score minus the baseline score. See Section B(3.3) of this review and statistical analysis plan regarding details on AUC approach.*

SF-12 PCS

The SF-12 scores are obtained using the Optum (PRO CoRE 1.3 Smart Measurement® System) software with the 2009 U.S. general population t-scores applied.

PGIC

This submission did not include documentation on a scoring algorithm.

Reviewer's comment(s): *Per the Applicant, the PGIC data will be summarized descriptively with number and proportion of patients in each category.*

7 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- ☒ Copies of instruments
- ☒ Literature review and/or publications
- ☒ Documentation of expert input
- ☐ Qualitative study protocols and interview guides for focus group or patient interviews
- ☐ Chronology of events for item generation, modification, and finalization (item tracking matrix)
- ☐ Synopsis of qualitative findings
- ☒ Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
- ☐ Quantitative summary report with evidence to support item retention and scoring
- ☐ Transcripts, if available

Tables 6 and 7 document the adequacy of the content of the COAs.

Table 6. Review of Content Validity for BPI-Item 3

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☒ Yes ☐ No	☒ Literature ☒ Clinical input e.g. discussion with clinical reviewer	Not applicable
Content validity	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☒ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☒ Target sample for qualitative research is appropriate. ☒ Studied sample for qualitative research adequately represents the target patient population ☒ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☒ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☐ COA is culturally adapted and adequately translated ☐ Descriptive statistics (if available) support content relevance ☒ Other (see Reviewer's comments)	See Section 6.3.1.1 of Appendix 3 of the Patient Symptom and Experience Report

Reviewer's comment(s): *The sponsor's qualitative work was specific to AIP patients, which is a specific subtype of AHP and the most common AHP type. Note that the indication will be for AHP and not any specific subtype. Based on literature and discussion with Clinical, pain is a relevant and important concept to AHP patients. From the qualitative report it appears that pain (including abdominal pain and general pain) is a relevant and important concept to AIP patients (in both acute attacks of porphyria and chronic porphyria).*

Review of the externally led patient focused meeting held on March 1, 2017 indicated that patients struggled with porphyria attacks, which caused severe, debilitating symptoms, extreme neuropathic pain, nausea, weakness to paralysis, confusion, hyponatremia and fatigue. Per the Voice of the Patient report, these symptoms became chronic over time in most of the patients.

Table 7. Review of Content Validity for SF-12 PCS

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☒ Yes ☐ No	☒ Literature ☐ Clinical input e.g. discussion with clinical reviewer	Not applicable
Content validity	☐ Yes ☒ Potentially – insufficient evidence available; additional information is needed ☐ No	☐ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☐ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☒ Target sample for qualitative research is appropriate. ☒ Studied sample for qualitative research adequately represents the target patient population ☐ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☐ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☐ COA is culturally adapted and adequately translated ☐ Descriptive statistics (if available) support content relevance ☒ Other (see Reviewer's comments)	See Section 6.3.2 of Appendix 3 of Patient Symptom and Experience Report

Reviewer's comment(s): *The most frequently reported impacts of AIP were related to sleep, inability to work, finances, difficulty walking, and decreased socialization.*

The Physical Functioning domain in the PCS consists of two items (question 2a and 2b) in the SF-12 that measure limitations in 1) performing moderate activities (e.g., vacuuming, moving a table, golfing) due to his or her health or in 2) climbing stairs. As reported in Appendix 3 (Qualitative Research Report) of the Patient Symptom and Experience Report, AIP patients characterized sensory neuropathy (e.g., numbness, tingling) and motor neuropathy (e.g., muscle weakness, paralysis, drop foot, unresponsive hands) as physical impacts, while mobility and exercise were characterized as impacts associated with sensory neuropathy. Therefore, the two items of the Physical Functioning domain may likely be of less importance to

patients (and may not be relevant for many AIP patients who may not engage in these activities) when evaluating givosiran's treatment effect.

The Bodily Pain and Role Physical domains appear to be more relevant and important to the daily lives of AIP patients than the Physical Functioning domain. The Bodily Pain domain contains one item and measures the amount of interference with normal activities due to pain. The Role Physical domain contains two items and measures physical health-related limitations to work or normal activities with lower scores indicating problems with activities due to physical problems.

For future development, it may be best to specify the domains of that are most relevant to the target population rather than using a summary score that combines relevant and non-relevant domains.

8 OTHER MEASUREMENT PROPERTIES

This submission did not include documentation on the other measurement properties of the BPI Item 3 and SF-12 PCS.

Reviewer's comment(s): *The other measurement properties of the BPI Item 3 and SF-12 PCS has been well-documented in literature.*

9 INTERPRETATION OF SCORES

To date, the following information has been submitted (check all that apply):

- ☐ Anchor-based analyses
- ☒ Anchor-based empirical cumulative distribution function (eCDF) curves
- ☒ eCDF study arm curves (Treatment vs. Placebo/Active Comparator)
- ☒ Anchor-based probability density function (PDF) curves
- ☐ PDF study arm curves (Treatment vs. Placebo/Active Comparator)
- ☐ Qualitative support for meaningful change (e.g., patient input)

Tables 8 and 9 documents the adequacy of the score interpretability of the COAs.

Table 8. Review of Score Interpretability for BPI-SF Item 3

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	☐ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☒ No	☐ Appropriate global anchor scales were included for anchor-based analyses ☐ Threshold(s) for within-patient meaningful change identified (anchor-based methods) ☐ Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves)	Applicant response to IR (Sequence # 0020)

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
		☐ Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) ☒ Other (see Reviewer's comments)	

Reviewer's comment(s): *Based on the eCDF curves (treatment vs. placebo), half of the patients who experienced a threshold of pain severity of 2 and 3 at baseline, reported approximately a 1-point change on the BPI-SF Item 3. Generally, the acceptable threshold for pain intensity is at least a 2-point change based on literature and what has been previously accepted in other Divisions. Approximately 20% of patients who experienced a threshold of pain severity of 2 and 3 at baseline, reported a 2-point change on the BPI-SF Item 3. It is unknown whether a 1-point change is a meaningful within-patient change for this target population. The anchor-based eCDF curves were not interpretable, as there was a lot of overlap between the favorable and non-favorable anchor response categories. Further, the PGIC had deficiencies (concept of interest was overall health status, recall error).*

Table 9. Review of Score Interpretability for SF-12 PCS

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	☐ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☒ No	☐ Appropriate global anchor scales were included for anchor-based analyses ☐ Threshold(s) for within-patient meaningful change identified (anchor-based methods) ☐ Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) ☐ Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) ☒ Other (see Reviewer's comments)	Applicant response to IR(Sequence # 0020)

Reviewer's comment(s):
Because some of the domains were not relevant to the target population and did not contribute to the PCS score change, it is difficult to interpret the eCDF curves.

D. APPENDICES

Appendix A: Brief Pain Inventory-Short Form Item 3 (BPI-SF Item 3)
Appendix B: 12-item Short Form Health Survey (SF-12)
Appendix C: Patient Global Impression of Change (PGI-C)

Appendix A
Brief Pain Inventory-Short Form Item 3 (BPI-SF Item 3)

Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.										
0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Appendix B
Short Form 12 (SF-12)

The SF-12 is a generic health-related quality of life questionnaire.

Figure 5.6. SF-12

	Excellent	Very Good	Good	Fair	Poor
In general, would you say your health is:					

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, How much?	Yes, limited a lot	Yes, limited a little	No, Not limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
Climbing several flights of stairs			

During the past 4 weeks, how much of the time have you had any of the following problems with your your work or other daily actitities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Accomplished less than you would like					
Were limited in the kind of work or other activities					

During the past 4 weeks, how much of the time have you had any of the following problems with your your work or other daily actitities as a result of any emotional problems (such as feeling depressed or anxious)	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Accomplished less than you would like					
Did work or other activities less carefully than usual					

	Not at all	A little bit	Moderately	Quite a bit	Extremely
During the past 4 weeks, how much did pain interfere with your normal work (including work both outside the home and housework)					

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to	All of the time	Most of the time	Some of the time	A little of the time	None of the time
the way you have been feeling. How much of the time during the past 4 weeks...					
Have you felt calm and peaceful?					
Did you have a lot of energy?					
Have you felt downhearted and blue?					

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?					

Appendix C
Patient Global Impression of Change (PGI-C)

Since the start of the study, my overall status is:						
1 Very Much Improved	2 Much Improved	3 Minimally Improved	4 No Change	5 Minimally Worse	6 Much Worse	7 Very Much Worse

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/s/

YASMIN A CHOUDHRY
10/30/2019 03:00:00 PM

SELENA R DANIELS
10/30/2019 03:01:13 PM

ELEKTRA J PAPADOPOULOS
10/30/2019 03:11:37 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 21, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212194
Product Name and Strength:	Givlaari (givosiran) injection, 189 mg/mL
Applicant/Sponsor Name:	Alnylam Pharmaceuticals, Inc. (Alnylam)
FDA Received Date:	October 16, 2019
OSE RCM #:	2019-1184-1
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Alnylam submitted revised carton and container labels for Givlaari (Appendix A). The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We reviewed the revised labels to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

We note that Alnylam proposes to keep the lot and expiration date on the bottom layer of the container label as it is on the portion of the bottom layer that is not overlapped by the top layer, and therefore, is visible at all times. As such, we have no further comment for the lot and expiration date. All other recommendations were accepted and implemented. DMEPA concludes the revised carton and container labels are acceptable from a medication error perspective. We have no additional recommendations at this time.

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[a] DeGraw, S. Label and Labeling Review for Givlaari (givosiran) NDA 212194. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 OCT 02. RCM No.: 2019-1184.

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/s/

STEPHANIE L DEGRAW
10/23/2019 03:24:52 PM

HINA S MEHTA
10/24/2019 10:26:13 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 15, 2019

To: Jennifer Lee, Regulatory Project Manager, Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for GIVLAARI (givosiran) injection, for subcutaneous use

NDA: 212194

In response to DHP's consult request dated June 27, 2019, OPDP has reviewed the proposed product labeling (PI) for the original NDA/BLA submission for Givlaari.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Jennifer Lee) on October 4, 2019, and are provided below.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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ROBERT L NGUYEN
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 2, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212194
Product Name and Strength:	Givlaari (givosiran) injection, 189 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Alnylam Pharmaceuticals, Inc. (Alnylam)
FDA Received Date:	November 15, 2018 and June 4, 2019
OSE RCM #:	2019-1184
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1. REASON FOR REVIEW

Alnylam Pharmaceuticals, Inc. submitted NDA 212194 Givlaari (givosiran) injection on November 15, 2018 as part of a rolling submission. Givlaari is a small interfering ribonucleic acid proposed for the treatment of acute hepatic porphyria (AHP) in adults (b) (4) . We evaluated the proposed container label, carton labeling, and Prescribing Information (PI) submitted on June 4, 2019, for areas of vulnerability that could lead to medication errors.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and PI for Givlaari to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the proposed PI identified the inclusion of (b) (4) that may be incorporated into the *Administration Instructions [2.2]* section of the PI. In addition, we identified areas in the PI, carton labeling and container label that can be modified to improve the clarity of the information presented.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI and labels can be improved to increase clarity of important information to promote the safe use of the product. We provide recommendations for the Division in Section 4.1 and recommendations for Alnylam in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Dosage and Administration [2]
   1. Administration Instructions [2.2] and (b) (4)
      a. We recommend revising the (b) (4) , and adding pertinent administration information to Section 2.2. We recommend revising this sections as follows:

GIVLAARI is intended for subcutaneous use by a healthcare professional only.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. GIVLAARI is a sterile, preservative-free, clear, colorless-to-yellow solution. It is supplied in a single-dose vial, as a ready-to-use solution that does not require additional reconstitution or dilution prior to administration.

Use aseptic technique.

- Calculate the required volume of GIVLAARI based on the recommended weight-based dosage *[see Dosage and Administration (2.1)]*.
- Withdraw the indicated injection volume of GIVLAARI using a 21-gauge or larger needle.
    - Divide doses requiring volumes greater than 1.5 mL equally into multiple syringes.
- Replace the 21G or larger needle with either a 25G or 27G needle with 1/2" or 5/8" needle length.
- Administer each injection at a different anatomic location (abdomen, the back or side of the upper arms, or the thighs) from the previous injection. An injection should never be given into scar tissue or areas that are reddened, inflamed, or swollen.
    - If injecting into the abdomen, avoid a 5.0 cm diameter circle around the navel.
    - If more than one injection is needed for a single dose of GIVLAARI, the injection sites should be at least 2 cm apart from previous injection locations.
- Discard unused portion.

B. How Supplied / Storage and Handling [16]
   1. How Supplied [16.1]
      a. We recommend including information about the color and other identifying characteristics of the product/solution (e.g., clear, colorless to yellow solution).

b. As currently presented, the NDC and strength is not provided. We recommend requesting the proposed NDC for review and adding the NDC and strength to the product description. For example, revise to read:

GIVLAARI is a clear, colorless to yellow ready-to-use solution available in single-dose vials of 189 mg/mL in cartons containing one vial (NDC XXXXX-XXXX-X).

4.2 RECOMMENDATIONS FOR ALNYLAM PHARMACEUTICALS

A. General Comments for the Container Label and Carton Labeling

1. We note the use of a placeholder for the NDC (i.e., 71336-XXXX-X). We request you submit your full proposed NDC for review.

2. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features and ensure that the established name is at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).

3. Revise "(b) (4)" to read "Injection" to accurately reflect the finished dosage form and align with the prescribing information.

B. Container Label

1. We recommend you include the lot and expiration date on the top layer of the label in accordance with 21 CFR 201.10(i).

C. Carton Labeling

1. As currently presented, a net quantity statement is not included. Please revise "(b) (4)" to read "1 single-dose vial".

2. We recommend revising "(b) (4)" to read "For subcutaneous injection by a healthcare provider only" to help alert patients and healthcare providers that the patient should take the product to their healthcare provider for administration.

3. To ensure consistency with the Prescribing Information, revise "(b) (4)" to read "Dosage: see prescribing information".

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Givlaari received on June 4, 2019, from Alnylam Pharmaceuticals, Inc..

Table 2. Relevant Product Information for Givlaari	
Initial Approval Date	N/A
Active Ingredient	givosiran
Indication	Treatment of acute hepatic porphyria (AHP) in adults (b) (4)
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	189 mg/mL
Dose and Frequency	2.5 mg/kg once monthly
How Supplied	Ready-to-use solution in a single-dose vial
Storage	Store at 2°C to 25°C (36°F to 77°F). GIVLAARI should be stored in its original container until ready for use.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of Failure Mode and Effects Analysis,[a] along with post-market medication error data, we reviewed the following Givlaari labels and labeling submitted by Alnylam Pharmaceuticals, Inc. on June 4, 2019.

- Container Label
- Carton Labeling
- Prescribing Information (no image shown)
  \\cdsesub1\evsprod\nda212194\0009\m1\us\114-labeling\draft\labeling\givlaari-givosiran-us-prescribing-information-word.doc

G.2 Labels and Labeling

Container Label

(b) (4)

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

STEPHANIE L DEGRAW
10/02/2019 12:14:55 PM

HINA S MEHTA
10/04/2019 11:48:23 AM

CLINICAL INSPECTION SUMMARY

Date	October 2, 2019
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Andrew Dmytrijuk, M.D., Medical Officer Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader Ann Farrell, M.D., Director Jennifer Lee, Pharm.D., Project Manager Division of Hematology Products
NDA	212194
Applicant	Alnylam Pharmaceuticals, Inc.
Drug	Givosiran
NME	Yes
Division Classification	RNA interference (RNAi) to inhibit synthesis of liver delta aminolevulinic acid synthase
Proposed Indication	Treatment of Acute Hepatic Porphyria in Adults (b) (4)
Consultation Request Date	June 27, 2019
Summary Goal Date	October 25, 2019 (Priority Review)
Action Goal Date	November 19, 2019
PDUFA Date	November 20, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites (Drs. Manisha Balwani, Montgomery Bissell, and Herbert Bonkovsky) and the sponsor's site were selected for inspection for Study ALN-AS1-003 in NDA 212194.

The study data derived from these clinical sites, based on the inspections, are considered reliable and the study in support of this application appears to have been conducted adequately.

The inspection of the sponsor's site found no deficiencies with oversight and monitoring of the trial. In general, the sponsor maintained adequate oversight of the clinical trial and appeared to be in compliance with Good Clinical Practice.

An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending Establishment Inspection Reports.

II. BACKGROUND

Givosiran acts via RNA interference (RNAi) to inhibit synthesis of liver delta aminolevulinic acid synthase 1 (ALAS1). The sponsor has proposed this NME drug (formulated for administration via subcutaneous injection) for the treatment of acute hepatic porphyria in adult (b) (4) patients.

A single study, ALN-AS1-003, will form the basis for the regulatory decision-making process for this application. The Division of Hematology Products requested inspection of three domestic clinical study sites. These sites enrolled patients that may have an impact in the review division's clinical decision-making process.

Study ALN-AS1-003

Study ALN-AS1-003 was a Phase 3, 2-part multicenter study designed to evaluate the efficacy and safety of givosiran in adults and adolescents (12 years and older) with a documented diagnosis of acute hepatic porphyria (AHP). The study included patients with acute intermittent porphyria (AIP) and other AHP types (Hereditary Coproporphyria [HCP], Variegate Porphyria [VP], and ALA dehydratase deficient porphyria [ADP]).

The primary study objective was to evaluate the effect of subcutaneous givosiran (ALN-AS1), compared to placebo, on the rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home in patients with acute intermittent porphyria.

The primary efficacy endpoint was the annualized rate of porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home in patients with AIP over the six-month treatment period.

The study was conducted in 36 active study centers. A total of 94 AHP patients: 46 patients (43 AIP) on placebo and 48 patients (46 AIP) on givosiran were enrolled and randomized. The study initiation date was December 7, 2017. The data cutoff date was January 31, 2019. The study is ongoing.

III. RESULTS (by site):

1. **Manisha Balwani, M.D., Site #401**
   One Gustave L. Levy Place, Box 1497
   Mount Sinai School of Medicine
   New York, NY 10029

   Inspection dates: August 26 to September 3, 2019

A total of four subjects were screened and enrolled. Four study subjects who received treatment completed the first double-blind part of the study. All four subjects are currently participating in an open-label extension part of the study. An audit was conducted for all enrolled subjects.

Source documents were verified against the case report forms and NDA subject line listings for study eligibility, informed consent form, IRB review/approval, monitoring, test article accountability, concomitant medication, delegation of authority, primary efficacy endpoint, and adverse event/serious adverse event reporting. Records review of the enrolled subjects indicated that the eligibility criteria for enrollment were met.

Source documents for the raw data used to assess the primary efficacy endpoint were verifiable at the study site. There was no under-reporting of adverse events. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. Montgomery Bissell, M.D., Site #404
513 Parnassus Avenue, Box 0538
San Francisco, CA 94143

Inspection dates: September 9 to 13, 2019

A total of five subjects were screened and enrolled. Five enrolled patients who received treatment completed the first double-blind portion of the study. All five subjects are continuing in the ongoing open-label extension part of the study.

For this inspection, a complete review of regulatory documentation at the study site was performed. Source records for the five subjects enrolled at the site were reviewed. The records reviewed included medical records, regulatory binder documents, delegation logs and signature logs, training logs, source data worksheets, informed consent forms, monitoring follow-up reports, and pharmacy records.

Source documents for all enrolled subjects were verified against the case report forms and NDA subject line listings for eligibility, adverse events, and serious adverse event reporting. Source documents for the primary efficacy endpoint raw data were verifiable at the study site. There was no under-reporting of adverse events.

There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

3. Herbert Bonkovsky, M.D., Site #405
Wake Forest Baptist Medical Center Outpatient Clinic
One Medical Center Blvd.
Winston-Salem, NC 27157

Inspection dates: August 19 to 22, 2019

A total of five subjects were screened and enrolled. Five study subjects who received treatment completed the first double-blind part of the study. Four subjects are currently participating in the open-label extension part of the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, site signatures and responsibility logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents, IRB approvals, and sponsor-generated correspondence were also reviewed.

Source documents for the five enrolled subjects were verified against the case report forms and NDA subject line listings for study eligibility, informed consent form documentation, primary efficacy endpoint, and adverse events/serious adverse event reporting. Records review of these subjects indicated that the eligibility criteria for enrollment were met.

Source documents for the raw data used to assess the primary efficacy endpoint were verifiable at the study site. Specifically, the number of porphyria attacks requiring hospitalization, urgent healthcare visit, or intravenous hemin administration at home were verified with the source documentation.

There was no under-reporting of adverse events. There were no limitations during the conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

4. Alnylam Pharmaceuticals, Inc.
300 Third Street
Cambridge, MA 02142

Inspection dates: September 17 to 20, 2019

This inspection evaluated compliance with the sponsor's responsibilities concerning the conduct of Study ALN-AS1-003. The inspection included review of organizational charts, vendor oversight, transfer of obligations, investigator agreements, financial disclosures, monitoring plans, monitoring reports, monitor qualifications, safety reports, adverse events, protocol deviations, and standard operating procedures. Monitoring Reports for Study ALN-AS1-003, specifically Sites 401, 404 and 405, were selected and reviewed. No underreporting of adverse events to the Agency was noted.

A Form FDA 483 was not issued at the end of the study inspection. In general, the sponsor appeared to be in compliance with Good Clinical Practice. Clinical trial oversight and monitoring by the sponsor appeared to be adequate.

{See appended electronic signature page}
Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Min Lu, M.D., M.P.H.
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/s/

ANTHONY J ORENCIA
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10/02/2019 01:57:41 PM

Division of Hematology Products Associate Director for Labeling Review of the Prescribing Information

Product Title	**GIVLAARI (givosiran) injection, for subcutaneous use**
Applicant	Alnylam Pharmaceuticals
Application/Supplement Number	212194
Type of Application/Submission[1]	NME
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s) (if applicable)	Treatment of acute hepatic porphyria (AHP) in adults (b) (4).
Approved Indication(s) (if applicable)	TBA
Date FDA Received Application	06/04/19
Review Classification (Priority/Standard)	Priority
Action Goal Date	02/04/2020
Review Date	08/16/19
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[2]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

The applicant is seeking approval of their new molecular entity, GIVLAARI (givosiran), an siRNA for the treatment of adults (b) (4) with acute hepatic porphyria.
This review is being completed during before mid-cycle.

In the attached PI, ADL comments (in balloons) are labeled with my name.

ADL recommendations provided in this review (e.g., recommended edits and comments regarding parts of PI) are preliminary and pending discussion with other review team members for this product.

[1] Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement
[2] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.
[3] See *PLR Requirements for PI* website for PLR labeling guidances.

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VIRGINIA E KWITKOWSKI
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Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 212194
Submission Number	009
Submission Date	6/1/2019
Date Consult Received	7/1/2019
Clinical Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND 126094 dated 06/02/2017 and 01/19/2018 in DARRTS;
- QTC analysis plan and report (Submission 0009);
- Study 003 protocol and clinical trial report (Submission 0009);
- Proposed label (Submission 0009);
- Highlights of clinical pharmacology and cardiac safety (Submission 0011).

1 SUMMARY

No large QTc prolongation effect (i.e., >20 ms) of givosiran was observed in this QT assessment.

The effect of givosiran was evaluated in Study ALN-AS1-003. The highest dose that was evaluated was 2.5 mg/kg once monthly, which is the therapeutic dose. The data were analyzed using central tendency analysis as the primary analysis, which did not suggest that givosiran is associated with large mean increases in the QTc interval (refer to section 4.3) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (section 3.1), exposure-response analysis (section 4.5), categorical analysis (section 4.4), and supporting data from Study ALN-AS1-004 (discussed in section 4.5).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Time	ΔΔ (ms)	90% CI (ms)
QTc	Givosiran 2.5 mg/kg	Day 1, 24 hr	2.5	(-2.1, 7.1)

Both givosiran and its major metabolite, AS(N-1)3' givosiran, have short half-lives and minimal accumulation with the once monthly dosing regimen. The sponsor's population PK analysis suggested that age and sex do not impact systemic exposure to givosiran and AS(N-1)3' givosiran and that the mean C_{max} values of givosiran and AS(N-1)3' givosiran are 34% higher and 16% higher, respectively, in East Asian patients compared to non-East Asian patients. The mean C_{max} values of givosiran and AS(N-1)3' givosiran are 9% higher and 36% higher in patients with moderate to severe renal impairment. The PK of givosiran is not affected by hepatic impairment or drug-drug-interaction with modulators drugs for CYP450 enzymes and/or drug transporters.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

None.

2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0009. Our changes are highlighted (addition, ~~deletion~~). This is a suggestion only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of givosiran on the QTc interval was evaluated in a double-blind, placebo-controlled study and the open-label extension in 94 patients. No large mean increase in QTc (i.e. > 20 ms) was detected at the 2.5 mg/kg once monthly dose level. (b) (4) [redacted] A dedicated thorough QT study has not been conducted with GIVLAARI.

Reviewer's comments: (b) (4) [redacted] *We propose to describe the study design and the number of subjects that supported the analyses.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Givosiran (also referred to as AD-60519, ALN-60519, or ALN-AS1; MW: approximately 17 kDa) is a synthetic, chemically modified, double-stranded siRNA that specifically targets 5-aminolevulinate synthase 1 (ALAS1) mRNA in the liver and is being developed for the treatment of acute hepatic porphyria (AHP). Givosiran drug product is composed of the drug substance siRNA conjugated to a triantennary GalNAc ligand to facilitate delivery to the liver. The proposed therapeutic dose is 2.5 mg/kg once monthly via subcutaneous (SC) injection

In a GLP safety pharmacology study in conscious, telemeterized male cynomolgus monkeys (Report AS1-NCD14-019), the effects of a single SC dose of 150 mg/kg givosiran had no effects on QT or other ECG parameters, hemodynamic parameters, respiration, and body temperature. Mean plasma concentrations of givosiran in this study at 6 and 24 hours postdose in monkeys were 13852 ng/mL and 1956 ng/mL, respectively,

which were 43- to 6-fold higher than the mean Cmax at the therapeutic dose in humans. An in vitro hERG assay with givosiran was not conducted.

Previously the QT-IRT reviewed a QT assessment proposal based on Study ALN-AS1-003 (under IND 126094, dated 01/19/2018 in DARRTS). At the time of the review, it was planned to have 70 patients randomized (1:1) in a double blinded manner to receive 2.5 mg/kg givosiran or placebo subcutaneously once per month. Triplicate 12-lead ECGs would be performed using centralized ECG services equipment. ECGs and time-matched PK would be collected at predose and 2-hours post-dose on Day 1, Month 5, and Month 6 visits, in all patients, and additional ECG and PK at 24-hour post-dose will be collected on Day 1 and Month 6 in approximately 24 patients. The analysis was designed to exclude large mean effects (i.e. 20 ms) at the therapeutic dose.

While the sponsor stated that a concentration-response evaluation for QTc would be conducted Phase 3 data and PK/ECG data from a DDI study, the QT-IRT was not able to determine adequacy of the concentration-QTc analysis plan because the analysis plan and the details of DDI study were not provided at the time of previous QT-IRT review. In addition, bioanalysis for the major metabolite was ongoing.

In the current submission, the sponsor conducted linear regression analysis and categorical analysis by pooling centrally assessed ECG data from studies ALN-AS1-003 and -004. PK/ECG data from Study ALN-AS1-003 included those from the 6-month double-blinded treatment phase (2.5 mg/kg) and the open-label treatment phase after the initial 6-month treatment (2.5 mg/kg and 1.25 mg/kg). Study ALN-AS1-004 was an open-label, DDI study in 10 patients with acute intermittent porphyria who are asymptomatic high excreters. PK/ECG data were collected before givosiran treatment (predose and at 1, 2, 4, 8, and 24 hours post-Inje probe cocktail administration on Day 1) and after givosiran treatment on Day 8.

The reviewers' analyses focus on Study ALN-AS1-003 only, because the study alone was designed to exclude large mean effect and because the sponsor did not provide justification (e.g. heterogenicity test) for data pooling. PK/ECG data from Study ALN-AS1-004 was considered as supportive evidence.

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

No large QT prolongation effect was found for givosiran. The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Not applicable. The analysis aims to exclude large effect.

3.2.1.1.1 QT bias assessment

Not applicable.

3.2.2 Categorical Analysis

No subject had post-baseline QTcF >480 ms or an increase from baseline in QTcF >60 ms in Study ALN-AS1-003. The results of the reviewer's analysis are similar to the sponsor's results for QTcF and ΔQTcF. Please see section 4.4 for additional details.

3.2.3 Safety Analysis

Study ALN-AS1-003: There were no patient deaths. SAEs were reported in 20.8% of patients in the givosiran group and 8.7% of patients in the placebo group. One patient ([redacted]) in the givosiran group had an SAE of abnormal liver function test leading to a protocol-specified discontinuation of study treatment and subsequent study withdrawal after completion of the 6-month DB period.

Reviewer's comment: *None of the SAEs were cardiac. There were no AEs related to QT prolongation, syncope, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, ventricular flutter, torsades de pointes, sudden death, or loss of consciousness.*

3.2.4 Exposure-Response Analysis

The sponsor did not conduct a formal exposure-response analysis. In the linear regression analyses using pooled data from two studies, the sponsor concluded an absence of correlation between ΔQTcF and plasma concentration of givosiran (slope [standard error]=0.002 [0.0027]) or its major metabolite (AS(N-1)3' givosiran, slope [SE]=0.005 [0.038]).

The reviewer's analysis using data from Study ALN-AS1-003 does not suggest a large mean effect on the QTc interval. The analysis is limited by the sparse sampling schedule which does not support an evaluation of potential PK/PD hysteresis. Please see section 4.5 for additional details.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate were observed (i.e., absolute mean change in HR <10 bpm; see Sections 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

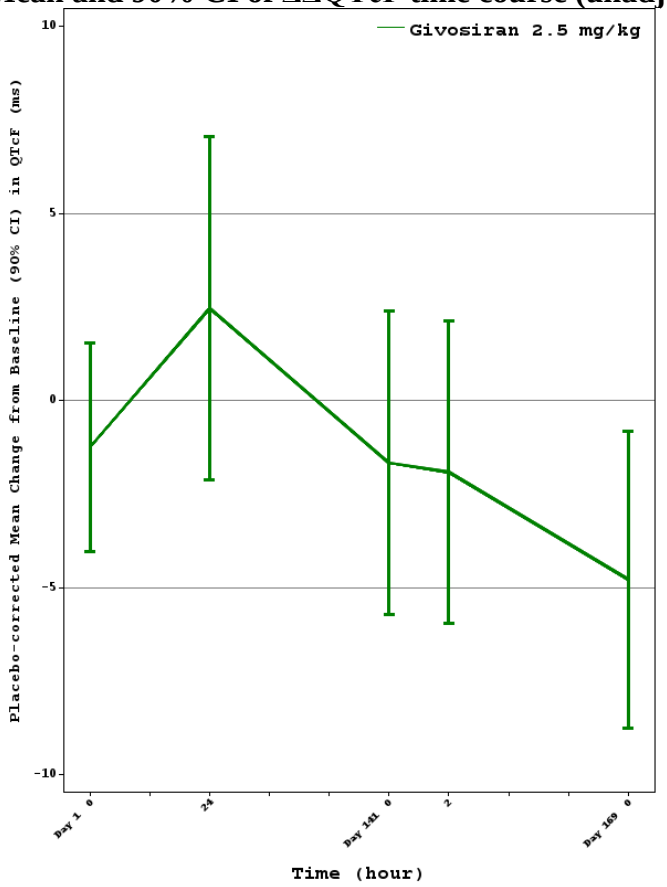
Not applicable.

4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The statistical reviewer used mixed model to analyze the ΔQTcF effect for the double-blind phase of Study ALN-AS1-003. The model includes treatment, time point, and treatment by time point as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The following figure displays the time profile of ΔΔQTcF for givosiran 2.5 mg/kg.

Figure 1: Mean and 90% CI of ΔΔQTcF time course (unadjusted CIs)



		ΔQTcF (ms) givosiran 2.5 mg/kg			ΔQTcF (ms) Placebo			ΔΔQTcF (ms)	
Day	**Time**	**N**	**LSmean**	**SE**	**N**	**LSmean**	**SE**	**LSmean**	**90% CI**
1	2	46	1.3	1.2	45	2.6	1.2	-1.3	(-4.0, 1.5)
	24	15	-0.2	2.0	17	-2.6	1.9	2.5	(-2.1, 7.1)
141	0	42	-0.3	1.7	44	1.4	1.7	-1.7	(-5.7, 2.4)
	2	42	1.0	1.7	44	3.0	1.7	-1.9	(-6.0, 2.1)
169	0	47	-0.3	1.7	46	4.4	1.7	-4.8	(-8.7, -0.8)

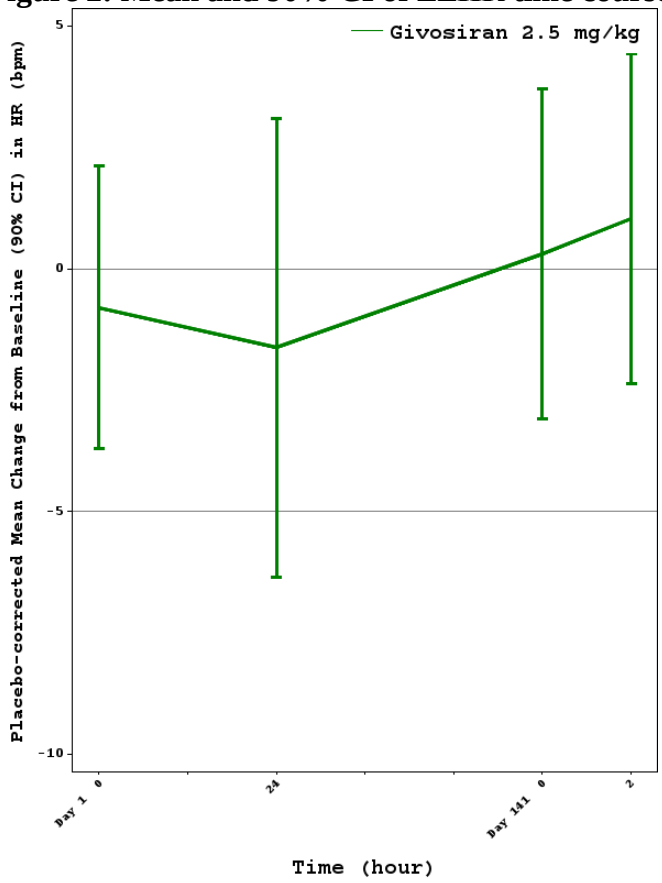
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

The same statistical analysis was performed for HR based on data from double-blind phase of Study ALN-AS1-003 (Figure 2).

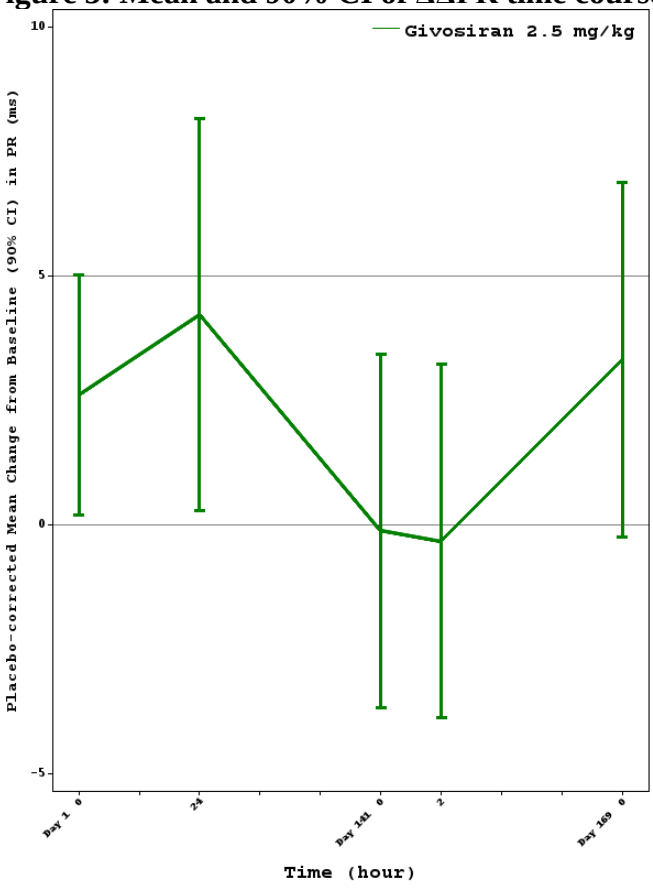
Figure 2: Mean and 90% CI of ΔΔHR time course



4.3.3 PR

The same statistical analysis was performed for PR interval based on data from double-blind phase of Study ALN-AS1-003 (Figure 3).

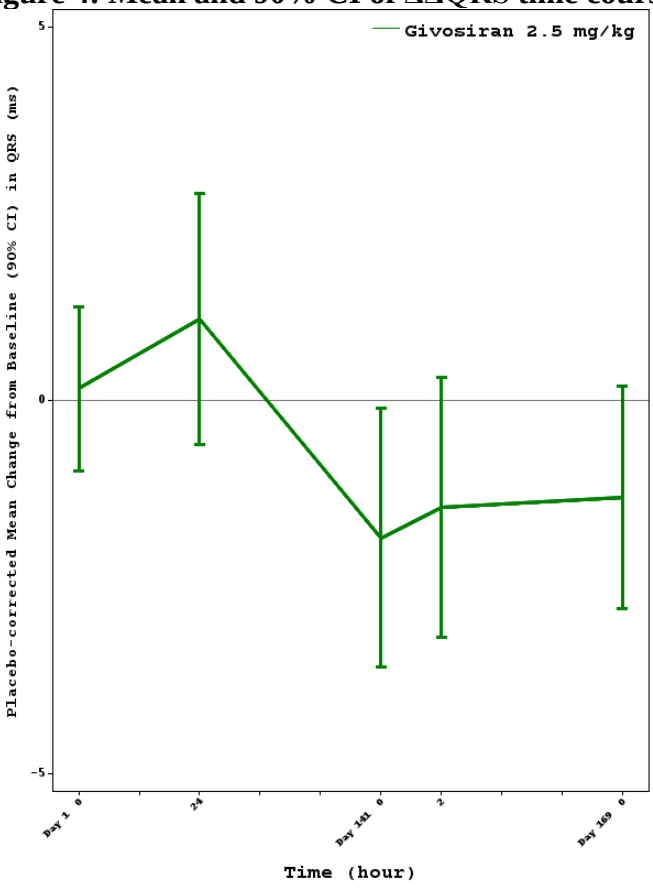
Figure 3: Mean and 90% CI of ΔΔPR time course



4.3.4 QRS

The same statistical analysis was performed for QRS interval based on data from double-blind phase of Study ALN-AS1-003 (Figure 4).

Figure 4: Mean and 90% CI of ΔΔQRS time course



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

Double-blind phase and open-label phase of Study ALN-AS1-003 were both included in categorical analysis. Table 2 lists the number of subjects as well as the number of observations whose QTcF values were ≤450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 2: Categorical Analysis for QTcF

Actual Treatment	Total (N)		Value <= 450 msec		450 msec < Value <= 480 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Givosiran 1.25 mg/kg	36	75	36 (100.0%)	75 (100.0%)	0 (0%)	0 (0%)
Givosiran 2.5 mg/kg	76	300	75 (98.7%)	297 (99.0%)	1 (1.3%)	3 (1.0%)
Placebo	46	209	44 (95.7%)	204 (97.6%)	2 (4.3%)	5 (2.4%)

Table 3 lists the categorical analysis results for ΔQTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 3: Categorical Analysis of ΔQTcF

Actual Treatment	Total (N)		Value <= 30 msec		30 msec < Value <= 60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Givosiran 1.25 mg/kg	36	75	34 (94.4%)	72 (96.0%)	2 (5.6%)	3 (4.0%)
Givosiran 2.5 mg/kg	76	300	74 (97.4%)	298 (99.3%)	2 (2.6%)	2 (0.7%)
Placebo	46	209	42 (91.3%)	204 (97.6%)	4 (8.7%)	5 (2.4%)

4.4.2 PR

The outlier analysis results for PR are presented in Table 4. No subject had PR >220 ms and an increase from baseline in PR >25% in Study ALN-AS1-003.

Table 4: Categorical Analysis for PR

Actual Treatment	Total (N)		Value <= 220 msec		Value > 220 msec & <= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Givosiran 1.25 mg/kg	36	75	36 (100.0%)	75 (100.0%)	0 (0%)	0 (0%)
Givosiran 2.5 mg/kg	76	300	75 (98.7%)	299 (99.7%)	1 (1.3%)	1 (0.3%)
Placebo	46	209	45 (97.8%)	207 (99.0%)	1 (2.2%)	2 (1.0%)

4.4.3 QRS

The outlier analysis results for QRS are presented in Table 5. No subject had QRS >120 ms in Study ALN-AS1-003.

Table 5: Categorical Analysis for QRS

Actual Treatment	Total (N)		Value <= 120 msec	
	# Subj.	# Obs.	# Subj.	# Obs.
Givosiran 1.25 mg/kg	36	75	36 (100.0%)	75 (100.0%)
Givosiran 2.5 mg/kg	76	300	76 (100.0%)	300 (100.0%)
Placebo	46	209	46 (100.0%)	209 (100.0%)

4.4.4 HR

The outlier analysis results for HR are presented in Table 6.

Table 6: Categorical Analysis for HR

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Givosiran 1.25 mg/kg	36	75	34 (94.4%)	73 (97.3%)	2 (5.6%)	2 (2.7%)
Givosiran 2.5 mg/kg	76	300	73 (96.1%)	296 (98.7%)	3 (3.9%)	4 (1.3%)
Placebo	46	209	41 (89.1%)	201 (96.2%)	5 (10.9%)	8 (3.8%)

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between ΔQTcF and givosiran or AS(N-1)3' givosiran concentrations using data from Study ALN-AS1-003. 36 patients who received placebo or 2.5 mg/kg givosiran treatment in the double-blinded period received 1.25 mg/kg givosiran treatment and contributed PK/ECG data on Day 1 of the open-label treatment period.

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship. Figure 2 shows an absence of significant changes in HR. Figure 5 shows the time-course of ΔΔQTcF and drug concentrations, and it does not show significant delayed effect at 24 hours postdose. However, the data do not support an evaluation of PK/PD hysteresis as only one ECG data was collected within 24 hour postdose. Figure 6 shows the relationship between ΔQTcF and drug exposure to givosiran or its major metabolite, and it generally supports the use of a linear model.

Figure 5: Time course of drug concentrations and QTcF. Time-points with < 5 subjects have been excluded from the plots.

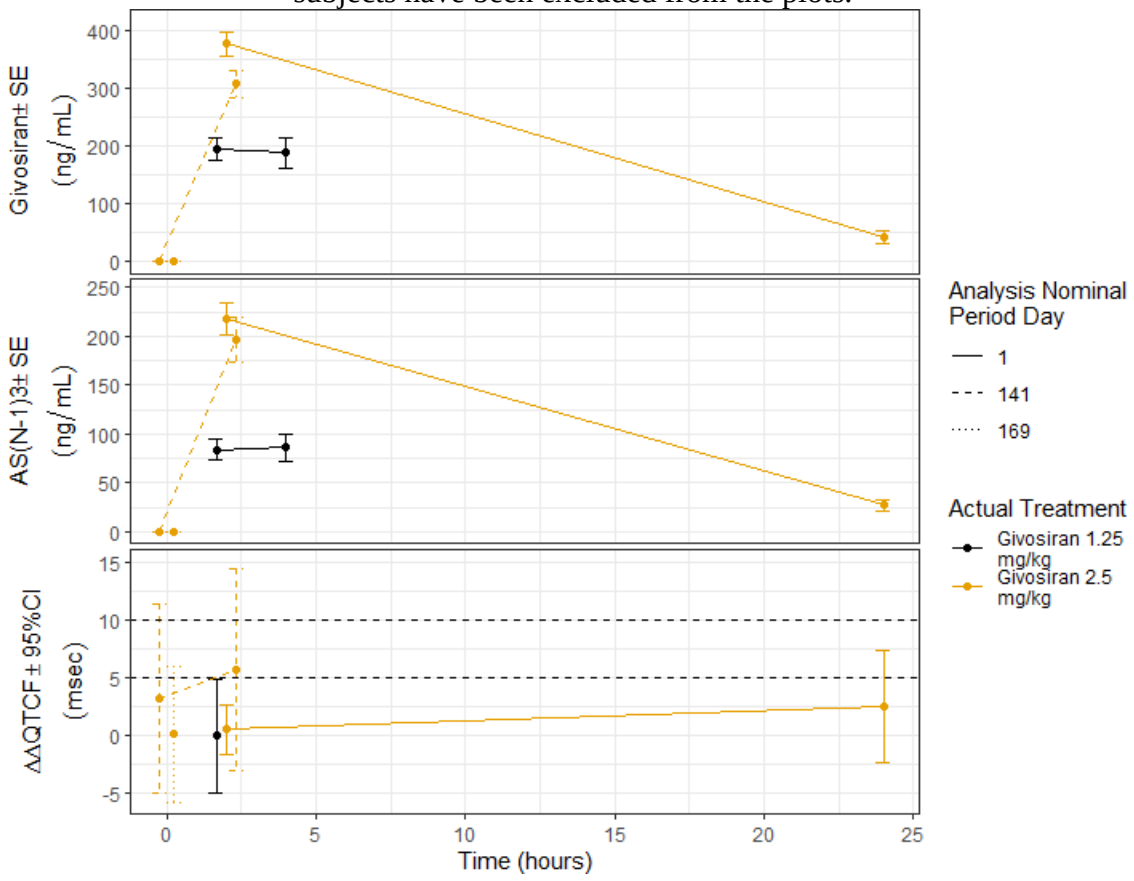
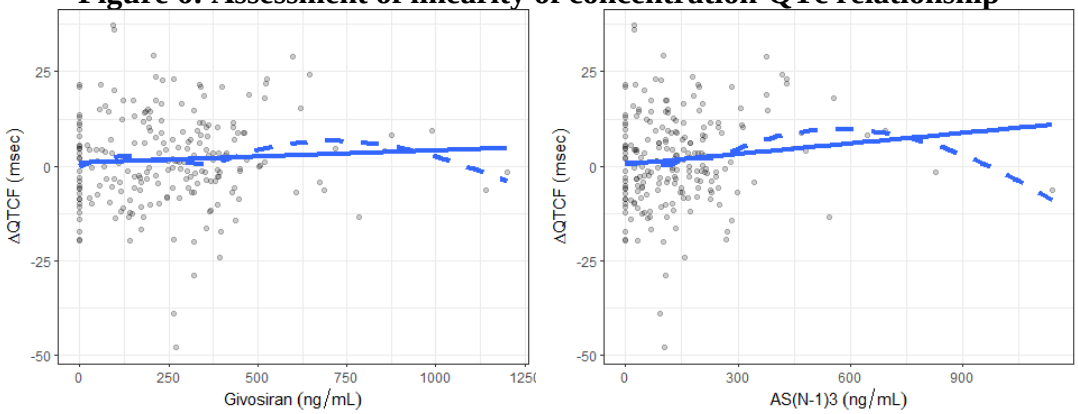
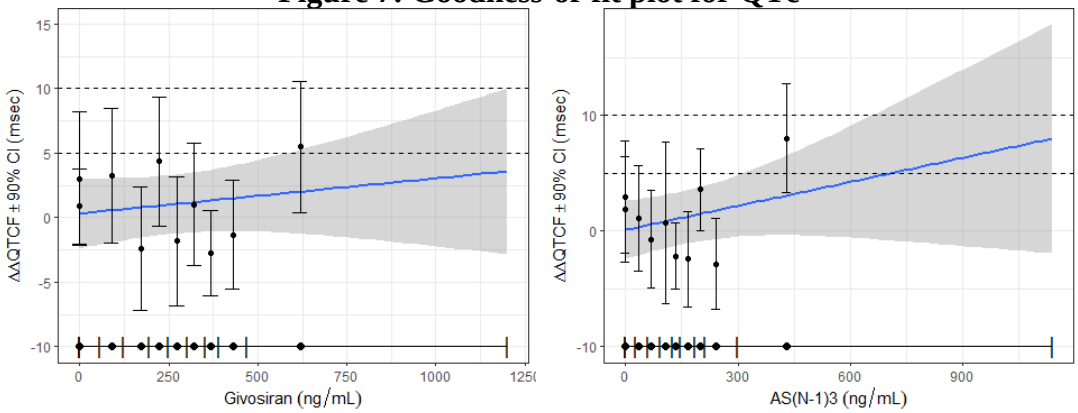


Figure 6: Assessment of linearity of concentration-QTc relationship



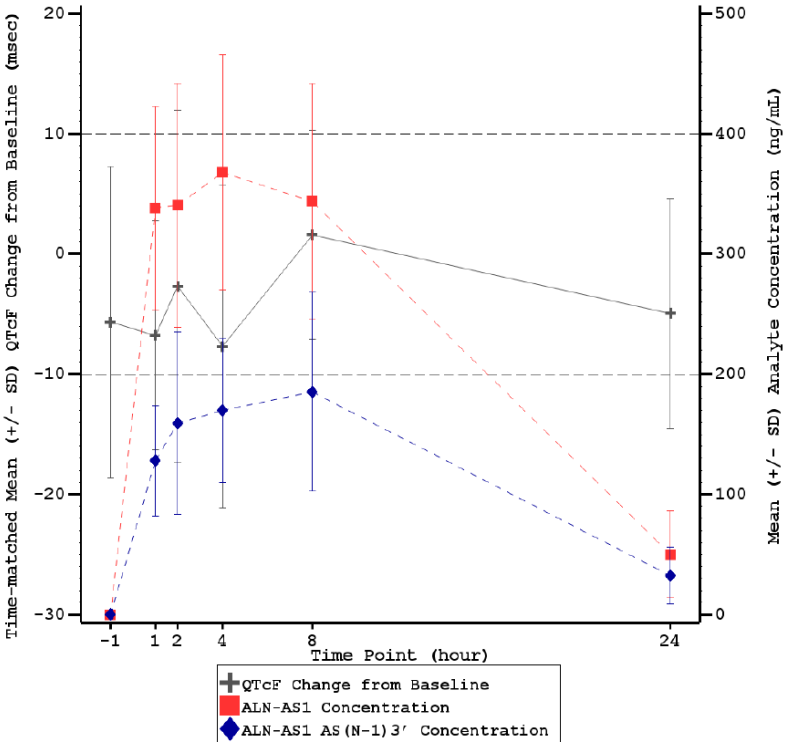
Finally, a linear mixed effect model (ΔQTcF ~ 1 + TRT + TIME + STUDYDAY + concentration + adjusted_baseline, with random subject effect on the intercept and slope) was applied to the data. The goodness-of-fit plot is shown in Figure 7. The analyses do not suggest large mean effect at the projected maximum exposure at the therapeutic dose (Cmax of givosiran: 359.2 ng/mL; Cmax of AS(N-1)3' givosiran: 199.5 ng/mL in Study ALN-AS1-003).

Figure 7: Goodness-of-fit plot for QTc



Study ALN-AS1-003 does not include PK/ECG data around Tmax of the major metabolite (i.e. ~8-hr postdose). However, PK data from Study ALN-AS1-004 suggests that the exposure of AS(N-1)3' givosiran at 2-hr postdose is not substantially lower than its Cmax (Figure 8 in QTC report, N=10). Based on available data on the concentration-QTc relationship, a large mean effect on the QTc interval is not expected around Tmax of AS(N-1)3' givosiran.

Figure 8: Study 004: Mean (±StDev) Change from Baseline QTcF and Plasma Givosiran and AS(N-1)3' Givosiran Concentration Versus Time



4.5.1 Assay sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.3. No additional safety analyses were conducted.

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/s/

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