CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217388Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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:	December 20, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217388
Product Name, Dosage Form, and Strength:	Wainua (eplontersen) injection, 45 mg/0.8 mL
Applicant Name:	Ionis Pharmaceuticals, Inc.
TTT ID #:	2022-3160-2
DMEPA 2 Safety Evaluator:	Ila Srivastava, PharmD
DMEPA 2 Team Leader:	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on December 18, 2023 for Wainua. The Division of Neurology 1 (DN 1) requested that we review the revised carton labeling for Wainua (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to a recommendation from the Office of Pharmaceutical Quality (OPQ) to align the listing of ingredients on the carton with the "Description" section of the prescribing information (PI).[a]

2 CONCLUSION

The revised carton labeling for Wainua is acceptable from a medication error perspective. We have no additional recommendations at this time.

[a] Cover Letter-Updated Carton Labeling for eplontersen NDA 217388.Carlsbad, CA: Ionis Pharmaceuticals Inc.; 2023 DEC 18. Available from: \\CDSESUB1\evsprod\NDA217388\0035\m1\us\cover-letter-sn0035-18dec2023.pdf

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/s/

ILA SRIVASTAVA
12/20/2023 10:59:33 AM

COLLEEN L LITTLE
12/20/2023 11:19:25 AM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	December 12, 2023
Reviewer:	Catherine Callahan, PhD, MA Division of Epidemiology I
Team Leader (Acting):	Sally Peprah, PhD, MSPH Division of Epidemiology I
Division Director:	CAPT Sukhminder K. Sandhu PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for study of safety of eplontersen exposure during pregnancy and lactation.
Drug Name:	Eplontersen (Wainua)
Application Type/Number:	NDA 217388
Applicant/Sponsor:	Ionis
TTT #:	2022-3159

A. Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Eplontersen is currently under review by the Division of Neurology 1 (DN1) for the proposed treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (ATTRv or hATTR). The mechanism of action for eplontersen is antisense oligonucleotide GalNAc conjugate that causes hepatic-targeted degradation of TTR mRNA (for mutant variants and wild-type TTR) through direct binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.[1]

ATTRy is a rare autosomal dominant disorder (>120 TTR gene mutations known) characterized by slowly progressive buildup of amyloid protein in the peripheral and central nervous systems, heart, kidneys, eyes, bone, and gastrointestinal tract
Death usually occurs 5 to 12 years after onset, most often due to cardiac dysfunction, infection, or cachexia. The exact incidence of hATTR amyloidosis is unknown and varies geographically, but is estimated to be 1/100,000 in U.S. Caucasians. Approximately 100 to 2500 individuals are estimated to have hATTR-PN in the United States.[2]

The recommended dosage of eplontersen is 45mg via subcutaneous injection by patient or caregiver once monthly. The proposed labeling for eplontersen contains a warnings and precautions statement for reduced serum vitamin A and recommends supplementation with the recommended daily allowance of vitamin A. [3]

1.2. Describe the Safety Concern

DN1 requested that the Division of Epidemiology (DEPI) assess the sufficiency of ARIA for a broad-based signal detection study of eplontersen exposure during pregnancy and lactation.

No formal studies of eplontersen in pregnant or lactating women have been performed. Pregnant or lactating women were excluded from participation in the eplontersen clinical studies, and women of childbearing potential were required to use acceptable methods of birth control throughout the study. As of the July 19, 2022, data cutoff date, there have been no reported pregnancies in the eplontersen clinical development program.

The draft labeling for eplontersen has the following information regarding pregnancy and lactation[4]:

[1] Eplontersen proposed labeling as of December 12, 2023
[2] Eplontersen NDA 217388, midcycle summary slides
[3] Ibid
[4] Ibid

8.1 Pregnancy

Risk Summary

There are no available data on WAINUA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. WAINUA treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking WAINUA. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. (b) (4) *[see Clinical Pharmacology (12.2) and Warnings and Precautions (5.1)].*

(b) (4)

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Subcutaneous administration of eplontersen (0, 5, 25, or 75 mg/kg) or a mouse-specific surrogate (25 mg/kg) to male and female mice weekly prior to and during mating and administration continued every other day in females throughout the period of organogenesis resulted in no adverse effects on embryofetal development.

8.2 Lactation

Risk Summary

There is no information regarding the presence of WAINUA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for WAINUA and any potential adverse effects on the breastfed infant from WAINUA or from the underlying maternal condition.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	

Identify unexpected serious risk when available data indicate potential for serious risk | X |

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
☐ No approved indication, but practitioners may use product off-label in pregnant women
☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review
☒ Other, please specify: Descriptive pregnancy safety study.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population
☐ Exposures
☒ Outcomes
☒ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population: ARIA lacks the capacity to identify lactating women.

Outcomes: ARIA lacks access to detailed narratives. Given that the study for broad-based surveillance being considered is descriptive and without a comparison group, having detailed narratives are deemed necessary to identify and validate outcomes, assess exposure-outcome temporality, and to conduct causality assessments.

Covariates: ARIA does not have detailed information on potential confounders. The descriptive pregnancy safety study being considered would collect detailed narratives with information on potential covariates, such as lifestyle factors and prenatal supplement use, including vitamin A supplementation.

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been fully tested and implemented in postmarketing surveillance of maternal and fetal outcomes. The ARIA analytic tools that assess drug use in pregnancy (and maternal and neonatal outcomes) currently include only women with a live-birth delivery.

2.5. Please include the proposed PMR language in the approval letter.

PMR 4564-1: Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to eplontersen during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

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/s/

CATHERINE L CALLAHAN
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SALLY A PEPRAH
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SUKHMINDER K SANDHU
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PATRICIA L BRIGHT
12/12/2023 11:20:14 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 29, 2023
To:	Justine Kankam, Regulatory Project Manager **Division of Neurology 1 (DN1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Aline Moukhtara, RN, MPH Team Leader **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert and Instructions for Use (IFU)
Drug Name (established name):	WAINUA (eplontersen)
Dosage form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 217388
Applicant:	Ionis Pharmaceuticals, Inc.

1 INTRODUCTION

On December 22, 2022, Ionis Pharmaceuticals Inc., submitted for the Agency's review New Drug Application (NDA) #217388 for WAINUA (eplontersen). The proposed indication for WAINUA (eplontersen) is treatment for polyneuropathy of hereditary transthyretin-mediated amyloidosis (ATTRv).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology 1 (DN1) on January 13, 2023, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for WAINUA (eplontersen) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft WAINUA (eplontersen) PPI and IFU received on January 13, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 20, 2023.
- Draft WAINUA (eplontersen) Prescribing Information (PI) received on September 13, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 20, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the PPI and IFU are consistent with the approved labeling where applicable.

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
11/29/2023 12:52:22 PM
DMPP-OPDP review of eplontersen (WAINUA) NDA 217388 DMPP-OPDP PPI and IFU

ALINE M MOUKHTARA
11/29/2023 01:03:57 PM

MARCIA B WILLIAMS
11/29/2023 01:40:31 PM

LASHAWN M GRIFFITHS
11/29/2023 01:55:24 PM

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

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

Memorandum

Date: November 28, 2023

To: Justine Kankam, Regulatory Project Manager, Division of Neurology 1 (DN1)

Laura Jawidzik, Clinical Reviewer, DN1

Tracy Peters, Associate Director for Labeling, DN1

From: Aline Moukhtara, Team Leader
Office of Prescription Drug Promotion (OPDP)

CC: Samuel Fasanmi, Regulatory Review Officer, OPDP

Subject: OPDP Labeling Comments for WAINUA™ (eplontersen) injection, for subcutaneous use

NDA: 217388

Background:
In response to DN1's consult request dated January 13, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for WAINUA™ (eplontersen) injection, for subcutaneous use.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 20, 2023, and our comments are provided below.

PPI, and IFU:
A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI and IFU, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on November 2, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

APPEARS THIS WAY ON ORIGINAL

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/s/

ALINE M MOUKHTARA
11/28/2023 07:27:13 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	November 9, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217388
Product Name, Dosage Form, and Strength:	Wainua (eplontersen) injection, 45 mg/0.8 mL
Applicant Name:	Ionis Pharmaceuticals, Inc.
TTT ID #:	2022-3160-1
DMEPA 2 Safety Evaluator:	Ila Srivastava, PharmD
DMEPA 2 Team Leader:	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 2, 2023 for Wainua. The Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Wainua (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Srivastava, I. HF Results and Label and Labeling Review for Wainua (NDA 217388). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 OCT 12. TTT ID No.: 2022-3162; 2022-3160.

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/s/

ILA SRIVASTAVA
11/09/2023 01:04:22 PM

COLLEEN L LITTLE
11/09/2023 02:24:06 PM

Clinical Inspection Summary

Date	10/31/2023
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Justine Kankam, Pharm.D., M.S., Regulatory Project Manager Monica Petluru, M.D., Medical Officer Laura Jawidzik, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
NDA #/BLA #	NDA #217388
Applicant	Ionis Pharmaceuticals, Inc.
Drug	Eplontersen
NME	Yes
Proposed Indication	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
Consultation Request Date	1/31/2023
Clinical Inspection Summary Goal Date	10/20/2023, extended to 11/3/2023
Priority/Standard Review	Standard
Action Goal Date	12/22/2023
PDUFA Date	12/22/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Coelho (Site #1817), Cruz (Site #1863), and Dasgupta (Site #1823), and the sponsor, Ionis Pharmaceuticals, Inc., were inspected in support of this NDA covering Protocol ION-682884-CS3. Based on the inspection results, the study appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

Primary efficacy data, modified Neuropathy Impairment Score +7 (mNIS +7) and secondary efficacy data, Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) were reviewed at the clinical investigator sites. No discrepancies were identified. Additionally, there was no evidence of under-reporting of adverse events.

II. BACKGROUND

Eplontersen injection for subcutaneous use is being developed for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults.

The sponsor has submitted one open-label Phase 3 study, ION-682884-CS3 (NEURO-TTRansform), to support the efficacy and safety of eplontersen for this indication. The statistical analysis supporting efficacy for this NDA is a comparison of eplontersen from this Phase 3 open-label study and placebo (external control) from a Phase 3 study (ISIS 420915-CS2 [NEURO-TTR]) previously submitted to support the efficacy and safety of inotersen (NDA 211172). These studies were similar in design. BIMO inspections covering Protocol ISIS 420915-CS2 (NEURO-TTR) were conducted when NDA 211172 was submitted.

Protocol ION-682884-CS3 [NEURO-TTRansform]

Title: "A phase 3 global, open-label, randomized study to evaluate the efficacy and safety of ION-682884 in patients with hereditary transthyretin-mediated amyloid polyneuropathy" *[Note: ION-682884 is eplontersen]*

Subjects: 168

Sites: 39 sites; Western Europe (13), North America (11), Latin America (8), Asia/Pacific (4), Australia (2), Middle East/Central Asia (1)

Study Initiation and Completion Dates: 12/11/2019 - ongoing

Data Cut-off Dates: 4/18/2022 (efficacy) and 7/19/2022 (safety)

This is an ongoing, open-label, randomized study of eplontersen in subjects with hereditary transthyretin-mediated amyloid (hATTR) polyneuropathy. Main inclusion criteria were males or females; 18 to 82 years of age; and hATTR polyneuropathy defined by meeting all of the following criteria:

- Stage 1 (ambulatory without assistance) or Stage 2 (ambulatory with assistance) according to the Familial Amyloid Polyneuropathy or Coutinho Stage
- Documented genetic mutation in the TTR gene
- Symptoms and signs consistent with neuropathy associated with transthyretin amyloidosis, including Neuropathy Impairment Score (NIS) $\geq$10 and $\leq$130

The study was comprised of three periods: Screening/Baseline Period, Treatment Period, and Post-Treatment Evaluation Period.

Screening/Baseline Period (Weeks -10 to -1)
The screening phase included study procedures to determine subject eligibility including, but not limited to physical examination, ECG, labs, transthyretin (TTR) genotyping, and

serum TTR. The Neuropathy Impairment Score (NIS) was obtained at screening and the modified NIS plus 7 (mNIS+7) was obtained at baseline.

Treatment Period (Weeks 1 to 85)
Subjects were randomized (6:1) to one of the following open-label study arms:

- Eplontersen 45 mg subcutaneously (SC) once every 4 weeks
- Inotersen 300 mg SC once every week

In addition to the investigational product (IP), subjects also took daily supplemental doses of vitamin A (approximately 3000 IU). Vitamin A deficiency was monitored via a screening questionnaire (ocular questionnaire).

Inotersen was included as a reference arm. The comparison for the efficacy analysis was the eplontersen arm compared to an external placebo arm from a prior protocol (see Background). Subjects in the inotersen arm crossed over to eplontersen once they completed Week 35 assessments. All subjects continued dosing with eplontersen until Week 81. End-of-treatment assessments were conducted at Week 85, 4 weeks after the last dose of investigational product.

For subjects randomized to eplontersen, there were a total of 43 visits during this study period. Eleven of the 43 visits were mandatory in-clinic visits, the remaining visits could be completed either in-clinic, at home by a home health-care provider (if approved locally), or by using a local laboratory upon investigator approval. For subjects randomized to inotersen, there were a total of 60 visits during this study period. Eleven of the 60 visits were mandatory in-clinic visits, the remaining visits could be completed at locations as above.

Post-Treatment Evaluation Period (Weeks 89 to 105)
Subjects not participating in an open-label extension study entered the 20-week Post-Treatment Evaluation Period.

The *co-primary efficacy endpoints* were the percent change from baseline in serum TTR protein concentration and mNIS+7. The key secondary efficacy endpoint was the change from baseline in the Norfolk Quality of Life-Diabetic Neuropathy scale (QOL-DN). The comparison for efficacy was eplontersen open-label data from Protocol ION-682884-CS3 compared to the external placebo cohort from Protocol ISIS 420915-CS2.

A pre-planned interim analysis was conducted at Week 35. Regardless of those results, the study was to proceed as planned with administration of eplontersen continuing until Week 66, the protocol-specified timepoint for the primary efficacy assessment. The Week 35 interim analysis demonstrated efficacy and are the data being submitted by the sponsor to support efficacy and safety. The protocol is ongoing.

III. RESULTS

1. Teresa Coelho, M.D.
Site #1817
Unidade Clinica de Paramiloidose
Hospital De Santo António
Porto, 4099-001
Portugal
Inspection Dates: 5/8/2023 – 5/12/2023

At this site for Protocol ION-682884-CS3 (NEURO-TTRansform), 26 subjects were screened, 25 subjects were enrolled, and 23 subjects completed the study. Four subjects were rescreened and enrolled after discontinuation and washout of tafamidis; one subject was rescreened and enrolled after recovering from COVID-19. Two subjects discontinued the study due to adverse events. Subject # (b) (6) randomized to inotersen, discontinued due to hyperthyroidism. Subject # (b) (6) randomized to inotersen, discontinued due to erythematous lesions on abdomen and right leg (injection sites) and drug eruption. Narratives for these subjects are included in the NDA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, IP accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, secondary efficacy data (Norfolk Quality of Life-Diabetic Neuropathy [QOL-DN]), and primary efficacy data (modified Neuropathy Impairment Score +7 [mNIS +7]). **The review division did not request verification of the other primary endpoint, serum TTR.**

The components of the mNIS +7, the primary efficacy endpoint, included the NIS, quantitative sensory testing (QST), autonomic function measured by the heart rate response to deep breathing, and the composite nerve conduction score (NCS). NIS scores were recorded in a paper Clinical Neuropathy Assessment booklet; QST and heart responses were conducted using an instrument (CASE IV) with printed results as source, and paper worksheets were completed for the NCS. The secondary efficacy data, QOL-DN, were recorded on paper source. The mNIS and QOL-DN source data were verified against sponsor data line listings for subjects receiving eplontersen since this is the group of interest compared to an external placebo group for the efficacy analyses. No discrepancies were identified.

There was no evidence of under-reporting of adverse events. One subject experienced a serious adverse event (SAE). Subject # (b) (6) randomized to eplontersen, was hospitalized due to skin infection (cutaneous infection of finger with extension to hand). The narrative for this SAE was included in the NDA submission.

2. Márcia Waddington Cruz, MD
Site #1863
Hospital Universitário Clementino Fraga Filho
Rua Professor Rodolpho Paulo Rocco 255
Rio de Janeiro, 21941-913
Brazil
Inspection Dates: 5/15/2023 – 5/19/2023

At this site for Protocol ION-682884-CS3 (NEURO-TTRansform), 21 subjects were screened (one subject screened twice), 21 subjects were enrolled, and 18 subjects completed the study. Subject # (b) (6) randomized to eplontersen, discontinued due to "withdrawal by subject". Subject # (b) (6) randomized to eplontersen, discontinued due to the SAE urosepsis. Narratives for these subjects are included in the NDA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, IP accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, secondary efficacy data (QOL-DN), and primary efficacy data (mNIS +7). **The review division did not request verification of the other primary endpoint, serum TTR.**

The mNIS +7 and QOL-DN source data were verified against sponsor data line listings for subjects receiving eplontersen since this is the group of interest compared to an external placebo group for the efficacy analyses. No discrepancies were identified.

There was no evidence of under-reporting of adverse events. Subject # (b) (6) randomized to eplontersen, experienced elevations in liver function tests (LFTs) on (b) (6) Study Day 351 (see Table 1). The next available labs in the NDA submission were for (b) (6) which showed normalization. However, according to the protocol (Section 8.5.1 safety monitoring rules for liver chemistry tests), labs were to be repeated within 48 to 72 hours to determine whether abnormalities were increasing or decreasing. When asked, the clinical investigator stated that, to obtain results more quickly, LFTs were repeated at a local lab within 72 hours of receiving and reviewing the elevated LFT results (see Table 1). These LFT elevations were reported as adverse events (transaminases increased). The sponsor submitted narratives for the category ALT/AST >3x upper limit of normal (ULN) which included this subject.

Reviewer comments: The CI followed the protocol with regard to repeating LFTs for Subject # (b) (6) within 48 to 72 hours of receiving the laboratory results. The laboratory results from the local laboratory were not included in the sponsor's narrative.

Table 1. Liver Function Test Results for Subject # (b) (6)

Date	ALT (U/L) [*RR 10–53 U/L]	AST (U/L) [*RR 14–43]	Total Bilirubin (mg/dL) [*RR 0.25-1.21]	GGT (U/L) [*RR 11 – 52]
(b) (6) [central lab]	431	644	1.43	NA
(b) (6) [local lab]	122	38	0.94	118
(b) (6) [central lab]	38	23	0.98	65

*Reference range from central lab, NA = not available

3. Noel Dasgupta, MD
Site #1823
Indiana University Health
550 North University Boulevard
AOC 5th Floor Room 5014
Indianapolis, IN 46202
Inspection Dates: 5/23/2023 – 5/25/2023

At this site for Protocol ION-682884-CS3 (NEURO-TTRansform), 8 subjects were screened and 5 subjects were enrolled, all of whom completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, IP accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, secondary efficacy data (QOL-DN), and primary efficacy data (mNIS +7). **The review division did not request verification of the other primary endpoint, serum TTR.**

The mNIS +7 and QOL-DN source data were verified against sponsor data line listings for subjects receiving eplontersen since this is the group of interest compared to an external placebo group for the efficacy analyses. No discrepancies were identified. Additionally, there was no under-reporting of adverse events.

4. Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010
Inspection Dates: 9/26/2023 – 9/29/2023

This inspection summary is based on communications with the ORA field investigator. The Establishment Inspection Report (EIR) is still pending. If, upon review of the EIR, significant issues are identified, this will be communicated with the review division and documented in an addendum to the Clinical Inspection Summary.

This inspection covered sponsor practices related to Protocol ION-682884-CS3 (NEURO-TTRansform) and focused on the three clinical investigator sites (Site #'s 1817, 1823, 1863) chosen for inspection.

Records reviewed during the inspection included, but were not limited to, SOPs, organizational charts, monitoring plan and reports, site selection/qualification, monitor qualification, vendor list, contracts and transfer of regulatory obligations (TOROs), investigator agreements and 1572s, investigator compliance/corrective actions, IRB approvals, eCRFs, data management, financial disclosure forms, pharmacovigilance procedures and documentation, quality assurance, protocol deviations, and IP accountability.

The sponsor contracted many of the study-related activities to a contract research organization (CRO), (b) (4) including project management, site identification and management, IRB submissions, safety reporting in the electronic data capture (EDC) system, IP management, clinical monitoring, and management of the Data Safety Monitoring Board (DSMB). The vendor, (b) (4) was responsible for data management. The sponsor provided oversight and retained most of the regulatory control.

Clinical monitoring at the sites was conducted by (b) (4) During the inspection, monitoring reports were reviewed for the three inspected sites. Significant protocol deviations identified during the monitoring visits were reported to the sponsor. According to the sponsor, no significant clinical investigator compliance issues occurred at the clinical sites. The sponsor's quality assurance audit plan was also reviewed with no issues identified.

The sponsor's pharmacovigilance (PV) group was responsible for ensuring that serious adverse events (SAEs) were evaluated and reported to the FDA per regulations. The PV group noted that the receipt and processing of SAEs was contracted to (b) (4) The PV group implemented monthly signal reviews, including signal detection, evaluation, and assessment. During the inspection, an audit of the SAE reconciliation reports was conducted with no issues identified.

The inspection did not note any deficiencies in the sponsor's control of IP. Final IP reconciliation has not been completed since only a few sites have been recently closed out.

{See appended electronic signature page}

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/s/

CARA L ALFARO
10/31/2023 11:40:00 AM

PHILLIP D KRONSTEIN
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JENN W SELLERS
10/31/2023 12:09:01 PM

HUMAN FACTORS STUDY REPORT AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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 5, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217388
Product Type:	Combination Product (Drug-Device)
Product, Name, Dosage Form and Strength:	Wainua (eplontersen) injection, 45 mg/0.8 mL
Device Constituent:	Autoinjector
Rx or OTC:	Prescription (Rx)
Applicant Name:	Ionis Pharmaceuticals, Inc.
FDA Received Date:	12/22/2022; 03/29/23; 07/21/23
TTT #:	2022-3162; 2022-3160
DMEPA 2 Safety Evaluator:	Ila Srivastava, PharmD
DMEPA 2 Team Leader:	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita Sterrett, PharmD
DMEPA 2 Director:	Danielle Harris, PharmD

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 217388 for Wainua (eplontersen) injection.

1.1 PRODUCT INFORMATION

Table 1 presents relevant product information for eplontersen that Ionis Pharmaceuticals, Inc. submitted on 12/22/2022.

Table 1. Relevant Product Information for eplontersen	
Initial Approval Date	N/A
Active Ingredient	eplontersen
Indication	Transthyretin-directed (b) (4) antisense oligonucleotide indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (ATTRv) in adults
Route of Administration	Subcutaneous
Dosage Form	injection
Strength	45 mg/0.8 mL
Dose and Frequency	45 mg once monthly
How Supplied	Carton containing one 45 mg single-dose autoinjector (AI)
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton protected from light. If needed, store at room temperature (up to 30°C [86°F]) in the original carton for up to 6 weeks; discard if not used within the 6 weeks.
Device Constituent (including figure)	Autoinjector ((b) (4) Device): (b) (4)
Intended Users	Adult patients with ATTRv amyloidosis, lay caregivers who care for individuals that cannot self-inject, and healthcare providers (e.g., registered nurses (RNs), nurse practitioners (NPs), and physicians).
Intended Use Environment	At home

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- In the written responses for the meeting request dated May 19, 2021 under IND 139521, we informed the Applicant to conduct a comprehensive risk analysis to

determine if a human factors validation study would be required for their proposed product.[a]

- On July 26, 2021, the Applicant submitted an HF validation study protocol under IND 139521. We completed our review of the HF validation study protocol and provided recommendations for the Applicant in the HF Advice Letter dated March 08, 2022.[b]
- On December 22, 2022, the Applicant submitted the results of the HF validation study under NDA 217388, which is the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2. Materials Considered for this Review

Material Reviewed	Appendix or Section
Product Information/Prescribing Information	Section 1.1
Background Information Previous DMEPA HF Reviews	A
Background Information on Human Factors Engineering (HFE) Process	B
Human Factors Validation Study Report	C
Information Requests Issued During the Review	D
Labels and Labeling	E

N/A=not applicable for this review

2 OVERALL ASSESSMENT HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

This section provides a summary of the study design, and our evaluation of the study methodology to determine if the study has been appropriately designed to evaluate and support the safe and effective use of the product.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants	• 16 injection-experienced adult (18+ years) ATTR amyloidosis patients or proxy patients

[a] Matthews, M. Final Written Response for eplontersen (IND 139521). Silver Spring (MD): FDA, CDER, OND, DN1 (US); 2021 MAY 19.

[b] Thambi, L. Human Factors Validation Study Advice Letter for eplontersen (IND 139521). Silver Spring (MD): FDA, CDER, OSE (US); 2022 MAR 08.

	• 15[c] injection-naïve adult (18+ years) ATTR amyloidosis patients or proxy patients. • 15 injection-experienced adult lay people who provide care to ATTR amyloidosis patients or proxy caregivers • 16 injection-naïve adult lay people who provide care to ATTR amyloidosis patients or proxy caregivers
Training	Participants were not trained.
Test Environment & Materials	The test room represented the basic characteristics of the intended use environment (e.g., typically a room within the home). The room was equipped with a table and any materials required to facilitate the hands-on use scenarios required of the participant (e.g., refrigerator, hand sanitizer, alcohol wipes, sharps container). The user interface was representative of the intend-to-market design and included the instructions for use (IFU), carton labeling, and autoinjector container label. Each autoinjector contained placebo solution (i.e., nonsterile water) instead of active drug product.
Sequence of Study	• Simulated Use scenario 1-Storage • Simulated Use scenario 2-Administer an injection (IFU optional) • Knowledge task 1-Storage • Knowledge task 2-Inspect product packaging • Knowledge task 3-Inspect autoinjector • Knowledge task 4-Allow autoinjector to warm to room temperature • Knowledge task 5-Select injection site • Final Interview/Root Cause Analysis (RCA)

2.2 DISCUSSION OF METHODOLOGY

Lack of HCP user group: As part of our previous HF protocol review under IND 139521,[d] we noted that the Applicant identified healthcare providers (HCPs) as intended users but did not plan to include HCPs as a distinct user group in the HF validation study. Therefore, we recommended that the Applicant revise the HF validation study protocol to include 15 HCPs who are representative of intended users or provide additional information to justify

[c] Per the Applicant, PN13 (a proxy patient participant) was disqualified after their test session due to their self-reported dexterity and vision impairments that were not representative of a proxy patient. The participant reported mild arthritis, no difficulties performing any tasks with their hands, and no vision impairments. Therefore, PN13's performance data was excluded from the HF report.

[d] Adeolu, A. Human Factors Validation Study Protocol Review for eplontersen injection (IND 139521). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 FEB 3. RCM No. 2021-1482.

excluding the HCPs user group. In the HF results report submitted under NDA 217388, the Applicant stated that the proposed autoinjector is intended for home use and is not anticipated to be administered by HCPs. From the Applicant: "It is expected that HCPs would prescribe the ION-682884[e] autoinjector to patients. Since ION-682884 is intended for home use, it is not anticipated to be administered by HCPs." The Applicant also stated that the proposed autoinjector device platform (i.e., (b) (4) is common in multiple products so it is anticipated that HCPs would be familiar with the device. The Applicant states there are no unique risks for the proposed product as compared to other approved autoinjectors that are intended for use by HCPs. While we disagree that HCPs are not anticipated to administer the proposed product (e.g., home nurse), we acknowledge that the proposed autoinjector is used in other marketed products by HCPs. Additionally, based on our routine postmarketing surveillance of these marketed products, we did not identify any safety signals specific to the HCP user group. As such, in this instance, we find the exclusion of HCPs acceptable.

Protocol deviations: Per the Applicant's IR response received on 03/29/23 (see Appendix D), the following deviations occurred during the execution of the HF validation study:

- Three patient participants were included in the injection-experienced user group as opposed to the injection-naïve user group even though it had been longer than 6 months since administering their last injection.[f] An additional two participants (one patient and one caregiver participant) were included in the injection-experienced group because although they performed injections years ago, they did so at a high frequency. We generally consider injection-experienced and injection-naïve participants to be distinct user groups. Additionally, we expect that each distinct user group in an HF validation study should have a minimum of 15 participants per user group (e.g., n=15 injection-naïve patients, n=15 injection-naïve patients, etc.).[g] In this case, although the protocol deviation resulted in a greater number of injection naïve participants and fewer injection experienced participants than intended, based on the participants injection experience and the time at which they performed their last injection, one could consider that these individuals may also be categorized as injection experienced. The Applicant stated that it is likely these participants still retained the knowledge required to successfully perform injections. In this case, we agree with the Applicant that this is acceptable and is unlikely to alter the results of the study since the users had performed many injections over many years and were familiar with multiple types of injection devices (e.g., syringes,

[e] Applicant described device constituent part ((b) (4) autoinjector)

[f] Based on the HF Validation study protocol submitted under IND 139521, "injection experienced" was defined as performed an injection within the last 6 months whereas "injection naïve" was defined as never performed an injection or did not perform an injection within the last 6 months for the patient and caregiver user groups.

[g] Guidance for Industry: Applying Human Factors and Usability Engineering to Medical Devices. Food and Drug Administration. 2016. Available from: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

pen injectors, etc.). Therefore, we find this study methodology does not preclude our review of the study results in this instance.

- Other deviations included using a sponge instead of an injection cushion at the beginning of Simulated Use scenario 2 and revising a use case scenario prompt to clarify the passage of time between storage and use of the autoinjector. We find these deviations are unlikely to impact performance of tasks in the HF validation study and therefore do not preclude our review of the study results.

Study Sequence: In the previous HF protocol review, we recommended the Applicant revise their HF study sequence as follows: simulated injection scenario, injection scenario root cause analysis (RCA), knowledge-based assessment (KBA), KBA RCA. In the results report, the Applicant indicated there was a single RCA at the end of the HF validation study. We find this does not preclude our ability to review the study results because this sequence does not impact participant performance or the interpretation of the results. Additionally, the Applicant has provided a root cause analysis and subjective feedback for each task assessed in the validation study.

3 RESULTS AND ANALYSIS

This section summarizes the errors/close calls/use difficulties observed in the HF study, and our analysis to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product.

We have carefully reviewed each observed issue, the Applicant's use-related risk analysis (URRA), the participants' subjective feedback, the Applicant's RCA, and the Applicant's comments and proposed mitigations (if applicable). Table 4 below provides a detailed analysis of certain observed issues where further discussion is warranted or where we identified areas of dissent with the Applicant's study report. Section 3.1 provides our high-level analysis of the observed issues where we agree with the Applicant's conclusions and have no further recommendations or comments.

Of note, one injection naïve patient participant (PN11) experienced errors with several tasks during Simulated Use Scenario 1, including:

- Remove cap
- Clean injection site
- Maintain autoinjector against injection site and monitor until delivery is completed
- Wash Hands
- Select injection site

The participant's subjective feedback indicated they did not notice the instructions in the carton because the IFU's cover did not look like instructions, thus, PN11 did not open or read the IFU. The Applicant concluded the root cause for all of the use errors performed by PN11 were attributed to the IFU cover being relatively nondescript, consisting only of a white background and plain black text which might have given the participant the impression that the document did not contain important information or instructions. We agree with the Applicant's

RCA and we have provided a recommendation in Table 5 for the Applicant to increase the prominence of the cover of the IFU.

Table 4. Detailed Analysis of Use Errors, Close Calls, and Use Difficulties and DMEPA's Recommendations

Legend: **UE** = use error; **CC** = close call; **UD** = use difficulty; **URRA** = use-related risk analysis; **RCA** = root cause analysis; **PX** = injection-experienced patient, **PN**= injection-naïve patient, **CX** = injection-experienced caregiver, **CN** = injection-naïve caregiver

Summary of Information Supplied by Applicant	DMEPA's Identified Areas of Dissent and Recommendations
Task: Activate the autoinjector by pressing against skin Scenario: Simulated Use scenario 2 Events: / Participant Type(s): UE (n=2) / PX (n=1), PN (n=1) CC (n=0) / UD (n=0) /	
Observed event(s): • Attempted to perform injection with cap attached • Removed rigid needle shield (RNS) from inside cap and placed inside device	
Risk associated with Task Errors (Per Applicant URRA): • Disease progression-requires medical intervention	
Relevant RCA/Subjective Feedback/Observation: • (b) (4) cap RNS ambiguous function • (b) (4) cap's open top • Thought RNS inside the (b) (4) cap was the needle so they reattached the (b) (4) cap to the autoinjector • Thought the RNS inside the (b) (4) cap was the needle they needed to attach because the RNS looked long and thin like a needle	
Applicant Comment and Proposed Mitigations: • The Applicant stated there are adequate instructions and design and that no additional mitigations are recommended. The Applicant referred to the participant performance for the task to remove the cap, where they revised the IFU to include the statement, "The needle is inside the orange needle shield".	The RCA and subjective feedback indicate that some participants believed the needle was located within the RNS and, therefore, the (b) (4) cap should stay attached to the AI while performing the injection or that the RNS should be removed and attached to the AI. The (b) (4) RNS is located inside the cap and has a long, thin appearance; however, the (b) (4) (b) (4). Additionally, the cap is described as the (b) (4) which may have led participants to believe (b) (4) (b) (4) We determined that the

<table>
<tr><td></td><td>Applicant's proposed mitigations for the task to remove the cap may not adequately address the use errors based on the RCA. Therefore, we find that the IFU can be further improved by revising the IFU images of the cap to accurately depict the RNS. Additionally, the description of the AI cap (e.g., (b) (4) can be improved to better convey that the AI cap (b) (4) (b) (4) This recommendation is consistent with IFU design for other approved products that use this device platform. We provide our recommendation below in Table 5. This recommendation can be implemented without the submission of additional HF data.</td></tr>
<tr><td>Task: Maintain autoinjector against injection site and monitor until delivery is complete
<u>Scenario</u>: Simulated Use scenario 2

<table><tr><td>Events:</td><td>Participant Type(s):</td></tr><tr><td>UE (n=6)</td><td>PX (n=3), PN[h] (n=2), CN (n=1)</td></tr><tr><td>CC (n=0)</td><td></td></tr><tr><td>UD (n=1)</td><td>CX (n=1)</td></tr></table></td><td></td></tr>
<tr><td>Observed event(s):
• Did not maintain against skin
• Moved device during injection
• Were unsure if they had administered the injection correctly</td><td></td></tr>
<tr><td>Risk associated with Task Errors (Per Applicant URRA):
• Laceration
• Delay in treatment, which might lead to an underdose. Per the Applicant, "this product is injected once monthly, an underdose or a single missed dose would not impact treatment. The half-life of the active ingredient in the body is sufficiently long enough such that a user would be able to get support and inject at the next available opportunity without impact to their treatment".</td><td></td></tr>
<tr><td>Relevant RCA/Subjective Feedback/Observation:</td><td></td></tr>
</table>

[h] One of these participants included PN11. Refer to section 3 of the review for additional information.

<table>
<tr><td>

- Reliance on user to know to position AI with window visible
- Rotated the autoinjector so they could see the viewing window and confirm that the orange plunger rod filled the entire window

</td><td></td></tr>
<tr><td>

Applicant Comment and Proposed Mitigations:

- The Applicant stated there are adequate instructions and design, no additional mitigation recommended. There are clear instructions in the IFU.

</td><td>The RCA and subjective feedback indicated that participants moved the device during the injection so that they could see the viewing window and confirm whether the orange plunger rod filled the entire window. The IFU does not state that users should (b) (4) . Therefore, we find IFU Step 6a-6c can be improved to indicate to users that they should ensure the viewing window of the device face them prior to injection. This statement is also present in other currently marketed IFUs of autoinjectors. We provide our recommendations below in Table 5. We find these recommendations can be implemented without the submission of additional HF data.</td></tr>
<tr><td>

Task: Dispose of autoinjector and cap
Scenario: Simulated Use Scenario 2

<table>
<tr><td>Events:</td><td>Participant Type(s):</td></tr>
<tr><td>UE (n=14)</td><td>CX (n=4), CN (n=6), PX (n=1), PN (n=3)</td></tr>
<tr><td>CC (n=0)</td><td></td></tr>
<tr><td>UD (n=1)</td><td>PN (n=1)</td></tr>
</table>

</td><td></td></tr>
<tr><td>

Observed event(s):

- Disposed of autoinjector in trash instead of sharps
- Difficulty understanding that the AI is single use

</td><td></td></tr>
<tr><td>

Risk associated with Task Errors (Per Applicant URRA):

- infection, localized/sharps waste

</td><td></td></tr>
<tr><td>

Relevant RCA/Subjective Feedback/Observation:

- Noted that the sharps container in IFU Step 8's illustration looks like (b) (4) . One participant explained this assumption was because the IFU's illustration (b) (4) . Another participant stated (b) (4) in the test room was red like the container depicted in IFU Step 8.

</td><td></td></tr>
</table>

Applicant Comment and Proposed Mitigations: • The Applicant stated, "to clarify the sharps container [redacted] the container in Step 5 will be [redacted]"	We determined that the proposed mitigations do not adequately address the identified task error based on the RCA. For example, some participants stated the illustration of the sharps container in IFU [redacted] Another participant added that because the IFU's illustration of the container did not have a [redacted] they thought [redacted] in the test room was red like the container in IFU Step 8. As such, we find the Applicant's post-validation revision of solely changing the color of the trash container does not address these use errors. The illustration of the sharps container in IFU Step 8 can be further improved to differentiate it from the trash. We provide our recommendation below in Table 5. We find this recommendation can be implemented without the submission of additional HF data.

3.1 ANALYSIS OF REMAINING IDENTIFIED ISSUES

The HF validation study showed use errors, use difficulties, and close calls with the tasks listed below:

- Store carton in refrigerator (Use Scenario)
- Store carton in refrigerator (Knowledge Check)
- Inspect packaging for damage or tampering (Knowledge Check)
- Check the product (drug) type and dose on the product packaging (Knowledge Check)
- Check the expiration date on the product packaging (Knowledge Check)
- Open package and remove autoinjector (Use scenario)
- Allow autoinjector to warm to room temperature (Use scenario and Knowledge Check)
- Inspect autoinjector for damage (Knowledge Check)
- Check the autoinjector (drug) type and dose (Knowledge Check)
- Inspect for expiration (on the autoinjector label) (Knowledge Check)
- Inspect drug (Knowledge Check)
- Wash hands (Use scenario)
- Select injection site (Knowledge Check)
- Clean injection site (Use scenario)
- Remove cap (Use scenario)

- Orient the autoinjector (perpendicular to skin) (Use scenario)

For each observed issue, we considered the participants' subjective feedback, the Applicant's URRA, RCA, and proposed mitigations (including any post-HFVS changes to the user interface), and the residual risk for each use-related event. For these issues, we determined the residual risk is acceptable and we have no further recommendations pertaining to these observed events.

4 LABELS AND LABELING

Tables 5 and 6 below include the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

Table 5. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information, Instructions for Use, Patient Information – General Issues			
1.	The prescribing information (PI), patient information (PPI), and Instructions for Use (IFU) include the placeholder "Tradename" instead of the conditionally acceptable proprietary name.	We refer to our Proprietary Name Request Conditionally Acceptable Letter dated September 6, 2023 letter stating the proprietary name, Wainua, is conditionally acceptable.	Replace "Tradename" with the conditionally acceptable proprietary name, "Wainua", throughout the PI, PPI, and IFU.
Full Prescribing Information – Section 2 Dosage and Administration			
2.	Section 2 of the PI states, (b) (4)	The statement as written may cause confusion about which injection sites are appropriate for caregivers. For example, the current statement may convey that caregivers (b) (4) which is inaccurate.	We recommend revising this statement so that it reads as follows: "Administer TRADENAME as a subcutaneous injection into the abdomen or upper thigh region. The back of the upper arm can also be used if a healthcare provider or caregiver administers the injection".
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	The product strength i.e., (b) (4)	(b) (4) with USP Chapter <7> (b) (4)	We recommend (b) (4)

	[redacted] (b) (4)	[redacted] (b) (4)	[redacted] (b) (4) the product strength reads “45 mg/0.8 mL”.
Instructions for Use			
1.	The subjective feedback in your HF validation study indicated that the instructions for use (IFU) were overlooked because the cover did not look like instructions.	We are concerned that users may not refer to the IFU when using the product which could result in medication errors.	Increase the prominence of this statement,” Instructions for Use” on the cover of the IFU for example by changing the color, increasing font size, or some other means.
2.	Several use errors occurred in the HF study where participants tried to reattach the autoinjector cap (i.e., [redacted] (b) (4)) prior to injecting the product because they confused the rigid needle shield (RNS) with a needle that required attachment.	Based on the use-related risk analysis (URRA), reattaching the autoinjector cap will lead to a failure to activate the dose and can result in disease progression which would require medical intervention. We are also concerned that the term [redacted] (b) (4) may convey to the user that the [redacted] (b) (4)	Revise the images in Steps 5a and 5c so that the autoinjector cap depicts the RNS and is representative of the to-be-marketed autoinjector cap. Additionally, replace the term [redacted] (b) (4) with a term that does not refer to the [redacted] (b) (4) (e.g., “cap” or “clear cap”) throughout your IFU.
3.	In the HF validation study, subjective feedback indicated that participants rotated or tilted the autoinjector to look at the viewing window during the injection.	We are concerned that if users aren’t able to see the viewing window prior to injection, they may lift the autoinjector before the injection is complete which may result in an underdose based on the URRA.	Update Step 6a of the IFU to add, “Make sure you can see the viewing window” after the statement, [redacted] (b) (4)

4.	In the HF validation study, subjective feedback demonstrated that some participants confused the image of the sharps container in IFU Step 8 (b) (4) (b) (4)	We acknowledge you updated the image in Step 5 of the IFU post-validation to address the use errors associated with the disposal task. However, we are concerned that the post validation change is insufficient to address the use errors because we are concerned that the container in Step 8 may still be misinterpreted as a (b) (4)	Revise the image of the sharps container in Step 8 so that the shape more closely resembles an FDA cleared sharps container. You may consider adding the caption, "Sharps Container" under the sharps disposal container in Step 8. Additionally, consider removal of the (b) (4) ((b) (4) image from Step 5 of the IFU to further minimize confusion.

Table 6. Identified Issues and Recommendations for Ionis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if

Table 6. Identified Issues and Recommendations for Ionis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.[i]
2.	The container label carton labeling, and Instructions for Use include the placeholder, "Tradename".	The proposed proprietary name, Wainua, was found conditionally acceptable on on September 6, 2023.[j]	Replace "Tradename" with the conditionally acceptable proprietary name Wainua throughout your labels and labeling.
3.	The "Store refrigerated" statement on the back panel of the container label and carton labeling lacks prominence.	Not including the "Store refrigerated" statement in bold may result in the risk of the storage information being overlooked and lead to deteriorated drug medication errors.	We recommend bolding the storage statements on container label and on the back of the carton to read "Store refrigerated at 2°C to 8°C (36°F to 46°F)".

[i] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2022. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[j] Thambi, L. Proprietary Name Request Conditionally Acceptable Letter for eplontersen. Silver Spring (MD): FDA, CDER, OSE (US); 6 SEP 2023. NDA 217388. https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806f13a0

5 CONCLUSION AND RECOMMENDATIONS

The results of the human factors (HF) validation study identified use errors, close calls, and use difficulties with critical tasks. Based on our review of the available participants' subjective feedback, and the Applicant's URRA, RCA, and proposed mitigations (including any post-HFVS changes to the user interface), we identified additional risk mitigations to address the use errors with labels and labeling.

Above, we have provided recommendations in Table 5 (for the Division) and Table 6 (for the Applicant). We ask that the Division convey Table 6 in its entirety to the Applicant so that recommendations are implemented within the current review cycle for NDA 217388. These changes can be implemented without submitting additional HF validation testing results for Agency review.

6 APPENDICES

APPENDIX A. PREVIOUS DMEPA REVIEWS

On March 3, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, eplontersen, IND 139521, and NDA 217388. Our search identified 1 previous relevant review[k], and we confirmed that our previous recommendations were implemented.

APPENDIX B. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessed in the HF results report. See Appendix C.

APPENDIX C. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessed in EDR via:

\\CDSESUB1\EVSPROD\nda217388\0001\m3\32-body-data\32r-reg-info\hfeue-summary-report-vv-qual-27179.pdf

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On 3/24/2023, we issued an Information Request (IR) to request readable and legible intend-to-market labels and labeling, a description of any protocol deviations that occurred during the HF validation study if applicable, and clarification about the labeling comprehension study. On 3/29/2023, the Applicant provided an acceptable response on that which can be accessed in EDR via:

\\CDSESUB1\EVSPROD\nda217388\0009\m1\us\1-11-1-response-to-ir-29mar2023.pdf

On 07/18/23, we issued an IR to request separate Word and PDF versions of the intend-to-market IFU as the IFU was embedded within the PI in the original NDA submission. We also asked the Applicant to confirm the layout of the intend-to-market IFU. On 07/21/23, the Applicant provided an acceptable response which can be accessed in EDR via:
\\CDSESUB1\EVSPROD\nda217388\0020\m1\us\cover-letter-sn0020-21jul2023.pdf

[k] Adeolu, A. Human Factors Validation Study Protocol Review for Eplontersen injection (IND 139521). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 JULY 26. RCM No.: 2021-1482.

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error experiences with similar products, we reviewed the following Wainua labels and labeling submitted by Ionis Pharmaceuticals, Inc.

- Container label(s) received on December 22, 2022
- Carton labeling received on December 22, 2022
- Instructions for Use received on July 21, 2023, available from \\CDSESUB1\EVSPROD\nda217388\0020\m1\us\1-14-1-3-eplontersen-ifu.pdf
- Prescribing Information and Patient Information received on December 22, 2022, available from \\CDSESUB1\EVSPROD\nda217388\0001\m1\us\1-14-1-3-eplontersen-uspi.pdf

E.2 Label and Labeling Images

Container label

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/s/

ILA SRIVASTAVA
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COLLEEN L LITTLE
10/05/2023 01:49:10 PM

LOLITA G STERRETT
10/05/2023 01:57:25 PM

DANIELLE M HARRIS
10/12/2023 09:11:46 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 25, 2023

TO: Teresa J. Buracchio, MD
Deputy Director
Division of Neurology I
Office of Neuroscience
Office of New Drugs

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
DGDSI/OSIS

SUBJECT: Remote regulatory assessment (RRA) of (b) (4) (b) (4)

1. RRA Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment (RRA) of the analytical portion of study ION-682884-CS21 (NDA 217388, Eplontersen Subcutaneous Injection, and conducted at (b) (4)

I did not observe any objectionable conditions during the RRA. Therefore, I conclude that data from the audited study are reliable.

2. Reviewed Study

Study#: ION-682884-CS21 (NDA 217388)

> "A Single-Dose, Randomized, Open-Label, 3-Period Crossover, Bioequivalence Study Comparing 3 Subcutaneous Formulations: Vial, Prefilled Syringe (PFS)with Safety Device and Autoinjector (AI) with ION-682884 in Healthy Adult Participants"

Clinical conduct date: (b) (4)
Sample Analysis Period:
Analytical Investigator:

3. Scope of RRA

OSIS scientist Xingfang Li, MD, RAC reviewed records of the analytical portion of the above study conducted at [redacted]

The RRA included an examination of records and processes for method validation and study sample analysis. The RRA included interviews with the firm's management and staff. In addition, the RRA included a virtual tour of the current facilities for receipt of samples, sample handling, sample storage, and bioanalysis.

4. RRA Observations

At the conclusion of the RRA, I did not observe any objectionable conditions. No items were discussed with the firm's management during the RRA close-out meeting.

Draft: XFL 09/23/2023
Edit: MFS 09/25/2023; KAB 09/25/2023

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/[redacted]

OSIS File #: BE9853
eNSpect Assignment #: 222194
eNSpect Operation #: 251304
FEI: [redacted]

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/s/

XINGFANG LI
09/25/2023 03:35:11 PM

MICHAEL F SKELLY
09/25/2023 03:44:24 PM

KIMBERLY A BENSON
09/25/2023 04:32:19 PM

Memorandum of Assessment

New Drug Application:	NDA 217388
Submission:	Seq. 0001 (SDN 1)
Subject:	Eplontersen (ION-682884) original new drug application; OBP immunogenicity assay validation assessment
Date Received:	22-December-2022; Request for Consultation issued by OND/DN1 on 03-August-2023
Assessment/Revision Date:	06-September-2023 / 21-September-2023
Primary Assessor:	Bruce Huang, CDER/OPQ/OBP/DBRRII
Secondary Assessor:	Weiming Ouyang, CDER/OPQ/OBP/DBRRII
RBPM:	Justine Kankam, OND/DN1
Consults:	n/a
Applicant:	Ionis Pharmaceuticals, Inc., Carlsbad, CA, USA
Product:	Eplontersen (ION-682884), antisense oligonucleotide (ASO) that specifically binds to and leads to degradation of TTR mRNA
Indication(s):	Treatment of transthyretin-mediated amyloidosis
Filing Action Date:	n/a for OBP immunogenicity assay validation assessment
Action Due Date:	19-October-2023 (OBP immunogenicity consult assessment desired completion date)

1. Summary Basis of Recommendation:

The anti-drug antibody assay is appropriately validated and suitable for detecting anti-drug antibodies against eplontersen in patient plasma samples from the clinical studies in this NDA submission.

2. Assessment:

Background/Product Description:

Hereditary transthyretin-mediated amyloidosis (ATTRv) is a fatal disease caused by autosomal dominant mutations in the gene that encodes for transthyretin (TTR) protein. Mutated TTR protein forms an unstable tetramer, which dissociates into TTR monomers and then aggregates into amyloid fibrils manifesting as polyneuropathy (PN) and/or cardiomyopathy (CM). The structure of eplontersen is a triantennary N-acetyl galactosamine (GalNAc3)-conjugated 2′-O-(2-methoxyethyl) [2′-MOE]-modified chimeric gapmer antisense oligonucleotide (ASO) with a mixed backbone of phosphorothioate (PS) and phosphodiester (PO) inter-nucleotide linkages. Eplontersen is an ASO inhibitor of human TTR protein synthesis, covalently linked to a ligand containing three N-acetyl galactosamine (GalNAc) residues to enable delivery of the ASO to hepatocytes. It has a sequence and mechanism of action identical to inotersen (TEGSEDI), a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of ATTRv in adults. The substitution of certain PS diester inter-nucleotide linkages in the wings of the ASO portion of eplontersen with PO diester inter-nucleotide linkages reduces the nonspecific protein binding and the immunoreactive properties of eplontersen compared to inotersen, and thus improves the tolerability of eplontersen compared to inotersen and reduces the incidence of injection site reactions (ISRs), as well as systemic adverse reactions such as flu-like symptoms.

Eplontersen targets and hybridizes to human TTR mRNA, resulting in ribonuclease H1 (RNase H1)-mediated degradation of the mRNA, inhibiting production of the TTR protein. Reduction of

TTR protein is theorized to decrease formation of TTR amyloid fibril deposits and thus slow, halt, or reverse disease progression.

Immunogenicity of eplontersen was evaluated in the Phase 1/2 study ION-682884-CS1 in healthy subjects and the Phase 3 study ION-682884-CS3 in diseased subjects with hereditary transthyretin-mediated amyloid polyneuropathy. Five of thirty-nine (12.8%) healthy subjects and 53 of 144 (36.8%) patients developed treatment-emergent ADA with Q4W administration of eplontersen for up to 13 and 85 weeks, respectively. There was no clinically meaningful impact of ADA positivity on PD, efficacy, or safety.

Immunogenicity validation assessment: Anti-drug antibody assay
Method: The Applicant used a three-tiered approach for their anti-drug antibody (ADA) testing strategy; the screening tier consists of identification of putative positive or negative samples, the confirmatory tier evaluates specificity of screened-positive samples, and the titration tier estimates the titer of ADA for confirmed positive samples to evaluate for any change in magnitude of the immune response over time.

The assay methodology consists of a qualitative enzyme-linked immunosorbent assay (ELISA) using a screening plate with ION-1146651 (3'-thiol labeled ION-682884) covalently linked to the surfaces of wells, and blocked with phosphate-buffered saline (PBS) containing 3% non-fat milk. After washing plates, positive control antibody (PC; anti-ION-682884 spiked in pooled normal human plasma [PNHP]), negative controls (NC), or analytical samples, are added at 1:50 minimum required dilution (MRD) in assay blocking buffer, for screening assay. After incubation and washing, ADA are detected by addition of Protein A/G-HRP (horseradish peroxidase) and TMB substrate, resulting in colorimetric reaction. Detection of the chromophore is achieved at 450 nm absorption, with the absorption being proportional to the level of ADA present in the plasma sample. The confirmatory ADA assay is performed in a similar fashion, with the addition of spiked ION-682884 drug (50 µg/mL final concentration, which is 100x concentration of ION-682884 plate-coating) as a competitor reagent. The confirmatory % inhibition due to the spike of 100-fold excess drug as compared to the plate coating concentration is calculated to confirm specificity of the ADA for the drug. Assay titration is also performed in a similar manner to the screening assay, with sequential 2-fold dilutions of the confirmed-positive samples, in order to determine the concentration beyond which the assay signal falls below the plate-specific titration cut point.

Assessor comment: The ADA assay methodology is reasonable, and similar in principle to other ELISA-based immunogenicity assay methodologies. It is not anticipated that any unusual issues would arise to cause adversity in the assay.

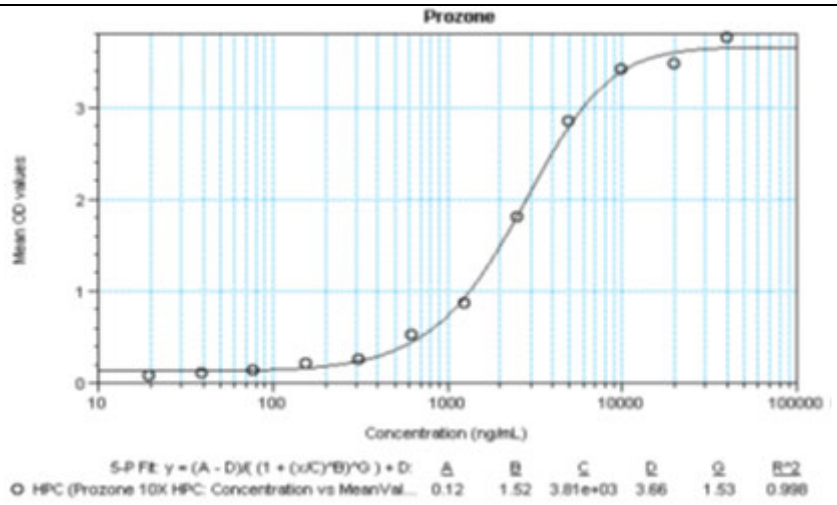
The Applicant did not include any validation materials for describing an assay designed for detecting anti-ION-682884 neutralizing antibody (NAb). The lack of a NAb assay for an oligonucleotide-based drug was addressed in association with the prior drug application for inotersen (NDA 211172), in the Immunogenicity Assay Consult Memorandum (OBP: H. Yan, B. Damdinsuren, and C. Downey; DARRTS Ref. ID# 4240723; signed 23-March-2018). In their NDA 211172 immunogenicity consult memorandum, it was commented that NAb assay assessment is not required for oligonucleotide products. The justification was rationalized by the consideration that due to the comparatively small size of oligonucleotides in comparison to immunoglobulin ADAs, it is regarded that all ADA would be neutralizing, because the binding of

ADA to an oligonucleotide drug would logically preclude the interaction of the drug with its target.

Assessor comment: *The justification for omitting a NAb assay in the current NDA 217338 is assessed to be reasonable according to the same rationale as that given for the prior oligonucleotide-based drug inotersen (NDA 211172).*

Assessor Table 1. Validation results and regulatory assessment for immunogenicity assay report Sponsor Reference No. 682884-MV06, Test Facility Study No. 3001809: Validation of an ELISA Method for the Detection of Anti-ION-682884 Antibodies in Human Plasma (Ionis Pharmaceuticals Inc., Carlsbad, CA, USA)

Validation Parameter	Results (Study No. 3001809)	*Assessor Comments*
Contract Research Org	(b) (4)	*None*
Assay principle	**Qualitative ELISA** method	*The indicated method is commonly used, and is acceptable.*
Sample Pretreatment (Acid dissociation)	**None** specified	*The Applicant did not indicate use of acid dissociation; however, sensitivity and tolerance of the assay appear adequate even without the use of an acid dissociation step. Additionally, the minimal required dilution (MRD) is relatively high, which further aids in reducing the possibility of interference by matrix components.*
Positive control (PC)	**Anti-ION-682884 Antibody**, Affinity Purified rabbit polyclonal IgG (Code: R-PC); (b) (4) Rabbit #28981, Lot 20A40004, 1.3 mg/mL, storage -20°C, expiration 15-Jan-2025	*The PC information is adequate, and the storage conditions are appropriate. Results from the specificity study indicate that the affinity purified anti-ION-682884 antibody specifically recognizes ASOs (ION-682884 (b) (4) and (b) (4) containing the (b) (4) moiety.*
Detection reagent	**Protein A/G-HRP conjugate** (1:50,000 dilution in wash buffer); Thermo Sci. #32490, Lot TH274567, 0.5 mg/mL, storage -20°C	*The detection reagent is appropriate.*
Depletion reagent	**ION-682884**, supplied by Ionis Pharma., Lot BSS-682884-02; 8.1 mg/mL, storage -20°C, re-testing date 25-Jan-2022	*The depletion reagent is appropriate for use in testing for confirmatory cut point and drug tolerance.*
Hook (Prozone) Effect	**No prozone was observed** in the tested range (≤40 µg/mL) or beyond (see graph, below); this is up to 10x of the HPC concentration of 4.0 µg/mL	*The absence of hook effect observation is acceptable to ensure that assay signal would not unexpectedly decline in the presence of ultra-high concentration of ADA.*



LPC1/LPC2	65 ng/mL and 100 ng/mL	*The PC concentrations are acceptable for modeling detection of ADA over adequately wide range of concentrations.*
MPC	1,500 ng/mL	
HPC	4,000 ng/mL	
Matrix and negative control (NC)	Normal human plasma (male/female), (b) (4) cat.#s HUMANPLK2MNN and HUMANPLK2FNN, Lots HMN14698 to HMN14732, HMN199325 to HMN199354 (Male); HMN14733 to HMN14767, HMN199355 to HMN199384 (Female); expiration 28 Feb 2024 (for HMN14698 to HMN14767), 30 Nov 2024 (for HMN199325 to HMN199384); storage in a freezer set to maintain -20°C Disease-State Human plasma (male/female), 109 individual lots: Disease-State Familial Amyloid Polyneuropathy (TTR); Sample ID#s too numerous to reproduce here, indicated in the assay validation report; storage in a freezer set to maintain -80°C	*The number of normal and diseased human plasma samples used is adequate for the immunogenicity assay validation.*
MRD	1:50	*The use of MRD to dilute samples may aid in minimizing non-specific signal from matrix components; the chosen MRD is appropriate based on assay validation results.*
Screening assay cut-point (SCP) factor, multiplicative	1.335 (fold of median NC OD; both normal and disease population); the SCP is plate-specific.	*SCP was determined using sixty lots of normal human plasma (30 males and 30 females) that were analyzed in duplicate on six occasions performed by two different analysts. The sample size is sufficient. The validation result for*

		SCP was calculated for one-sided 90% lower confidence limit for the 95th percentile, thus assuring at least 5% false positive rate (FPR) with 90% confidence; the FPR is appropriate for the SCP.
Confirmatory cut point (CCP)	36.5% inhibition (corresponding to a one-sided 80% lower confidence limit for the 99th percentile) assures at least a 1% false positive with 80% confidence.	*CCP was assessed within the same occasion as SCP. The validation result for CCP was calculated to assure at least a 1% FPR with 80% confidence; the FPR is appropriate for the CCP.*
Titer cut point (TCP)	1.679 (fold of median NC OD; both normal and disease population); the TCP is plate-specific.	*TCP was assessed within the same occasion as SCP. The validation result for TCP was calculated for one-sided 90% lower confidence limit for the 99.9th percentile, thus the FPR is 0.1%, which is acceptable.*
Assessor Comment: The applicant compared the SCP, CCP and TCP in normal and disease-state plasma using 30 lots of normal human plasma (15 males and 15 females) and 30 lots of disease-state human plasma (15 males and 15 females), which were analyzed in duplicate on a total of one occasion performed by two analysts (total of 2 runs). No statistically significant difference was observed between the results from normal and disease-state human plasma, supporting that the cut-points determined using normal human plasma could be considered applicable for the disease population.		
Sensitivity	Screening assay: 37 ng/mL Confirmatory assay: 63 ng/mL	*The assay sensitivity meets the Agency recommendation for sensitivity of better-than 100 ng/mL.*
Assay Drug tolerance	**≥65** ng/mL PC detection in 4.0 µg/mL ION-682884	*The clinical drug C_{max} is estimated to be 0.226 µg/mL (Section 2.7.2 Summary of Clinical Pharmacology Studies), which is below the 4.0 µg/mL drug level that the assay is able to tolerate, which is acceptable.*
Repeatability/Intra-assay variability	The repeatability assay measurements for the PCs were evaluated in duplicate, in six replicates, in two assays performed by two analysts. All results were found within the acceptance criteria of ≤20% CV for both screening and confirmatory assays at all PC concentrations and repeats; all %CV results for PC repeatability were found <7%.	*The AC for repeatability is reasonable, and the repeatability of the screening and confirmatory assay were both evaluated acceptably. The assay repeatability was found to be well within the AC requirement, demonstrating that repeatability of the assay is adequate.*
Intermediate Precision (IP)/inter-assay variability	The intermediate precision of the assay measurements was evaluated for the PCs at least in duplicate (total of at least four wells). The acceptance criteria for IP of both screening and confirmatory assays were ≤20% CV. All IP results were found within	*The AC for IP is reasonable, and the IP of the screening and confirmatory assay were both evaluated acceptably. The assay IP were found to be well within the AC requirement, demonstrating that IP of the assay is adequate.*

	the acceptance criteria for both screening and confirmatory assays at all PC concentrations and repeats.	
Selectivity	8/10 samples of un-spiked plasma were negative, while 9/9 plasmas spiked with LPC and 9/9 plasmas spiked with HPC were positive in screening and confirmatory setting.	*The selectivity evaluation data demonstrated acceptable results. The presence of occasional positivity in the un-spiked plasma is not an unexpected result, because of the false-positivity rate built into the assay, and it is acceptable.*
Hemolysis, Lipemia	- LPC and HPC samples were prepared in plasma containing 5% hemolyzed whole blood; NC samples read below the SCP and CCP, and all LPC and HPC samples were confirmed positive despite the hemolyzed blood in both screening and confirmatory assays. - In hyperlipidemic plasma, analysis of unspiked lipemic serum lots found 7 of 10 (70%) samples screened negative, while 8 of 8 LPC and 7 of 8 HPC screened positive in lipemic serum. In confirmatory assays, 8 of 10 unspiked lipemic serum lots were negative, while 8 of 8 LPC and 8 of 8 HPC confirmed positive.	*The assay was shown to be adequately tolerant to the presence of hemolytic and lipemic substances in the samples, which is acceptable for use in the immunogenicity assay.*
Stability	LPC and HPC samples thawed at room temperature for ≥4 hrs, then stored at room temperature for 24 hours; or eight cycles of freezing and thawing at bench-conditions; all tested samples returned results within the acceptable range of their titer.	*The stability results indicated that the control samples under the assay conditions are able to withstand several extremes of storage conditions, and freezing/thawing cycles, without significant loss of assay viability.*
Overall ADA assay assessment		*The results of the ADA assay validation exercises demonstrated that the assay is suitable for detection of ADA in patient samples collected during the course of the ION-682884 clinical trials.*

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/s/

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WEIMING OUYANG
09/21/2023 02:04:16 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM
INJECTOR DEVICE

Date	August 22, 2023
To:	ERICA KEAFER
Requesting Center	CDER
From	ALAN STEVENS OPEQ/OHT3/DHT3C
Through (Team)	Injection Devices Team OPEQ/OHT3/DHT3C
Subject	ICCR #00889329 ICC2201115 Submission: NDA217388 Drug Name: Eplontersen Indication for Use: treatment of polyneuropathy of hereditary transthretin-mediated amyloidosis (ATTRv) in adults.
Recommendation	**Final Recommendation Date:** ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments ☐ Device Constituent Parts of the Combination Product are Not Approvable (See CR Recommendations in Section 1)

Digital Signature Concurrence Table	
Reviewer	**Team**
	

1. SUMMARY RECOMMENDATIONS

The autoinjector performance data are acceptable and CDRH recommends approval.

2. PURPOSE/BACKGROUND

CDER is requesting review of the subject combination product that includes an injector device.

CDRH provided a facilities review under ICCR 00889333 / ICC2201116.

3. DEVICE DESCRIPTION

The device is supplied by (b) (4)

Figure 1: Eplontersen Autoinjector

	Multi-Dose Container	Single-Dose Container
Replaceable Container	☐ **A** Each container holds multiple doses, the size of which may be fixed or variable (set by the user).	☐ **B1** Each container holds a single dose, and the entire deliverable volume is expelled.
		☐ **B2**

		Each container holds a single dose, and a portion of the deliverable volume is expelled.
Non-replaceable Container	☐ **C** The container holds multiple doses, the size of which may be fixed or variable (set by the user)	☑ **D1** The container holds a single dose, and the entire deliverable volume is expelled.
		☐ **D2** The container holds a single dose, and a portion of the deliverable volume is expelled.

4. DEVICE SAFETY AND PERFORMANCE REVIEW

1. FDA Recognized Standards

☑ Device Conforms to ISO 11608-1:2014 (application received before the transition to ISO 11608-1:2022
☑ Needle Safety features conform to ISO 23908

2. Essential Performance Requirements

Essential Performance Requirement	Specification	Design Validation Y/N
Cap Removal Force	(b) (4)	Y
Activation Force		Y
Extended Needle Length		Y
Injection Time		Y
Dose Accuracy		Y

3. Design Verification Test Case Matrix

Test Case	Condition Tested		EPRs Tested		Probability Content (tests all have 95% CI)		Data Acceptable	
	Yes	N/A	All	Subset	ISO 11608-1	Other	Y	N
Cool	☒		☐	☒	☒97.5%	☐%	☒	☐

Standard	☒		☒	☐	☒97.5%	☐%	☒	☐
Warm	☒		☐	☒	☒97.5%	☐%	☒	☐
Last Dose Accuracy	☐	☒	☐	☐	☐97.5%	☐%	☐	☐
Life-Cycle	☐	☒	☐	☐	☐95%	☐%	☐	☐
Free fall	☒		☐	☒	☒95%	☐%	☒	☐
Dry Heat	☒		☐	☒	☒97.5%	☐%	☒	☐
Cold Storage	☒		☐	☒	☒97.5%	☐%	☒	☐
Damp Heat	☐	☒	☐	☐	☐95%	☐%	☐	☐
Cyclical	☐	☒	☐	☐	☐95%	☐%	☐	☐
Vibration	☒		☐	☒	☒95%	☐%	☒	☐
Transport	☐		☐	☐	☐95%	☐%	☐	☐
Functional Stability	☒		☒	☐	☐95%	☒97.5%	☒	☐
Fluid Leakage	☐	☒	☐	☐	☐95%	☐%	☐	☐

Reviewer Comments

- Per ISO 11608-1:2014, only dose accuracy is required to be tested to all preconditions listed. This was acceptable at the time of submission.
- EPRs tested on standard conditions. Also tested on stability and lifecycle preconditioning.
- Lifecycle preconditioning included combined preconditioning in the following sequence: cold storage, transit testing, cold storage, dry heat/room temp, standard temp.
- Functional stability assessed device storage for 2 years for subassembly followed by 3 years with final combination product. Accelerated testing was assessed in submission. Real time testing is ongoing.
- Accelerated aging assessed all EPR and needle safety functions.

4. Risk Analysis

☑ Risk Analysis conforms with ISO 14971:2019

5. Additional Performance Data

N/A

5. CONTROL STRATEGY

<<END OF REVIEW>>

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/s/

ERICA F KEAFER
08/22/2023 02:06:22 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 5, 2023

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead Cardiac Safety IRT, DCN

To: Justine Kankam, RPM
DN1

Subject: QT Consult to NDA 217388 (SDN #001)

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

This memo responds to your consult to us dated 1/20/2023 regarding the applicant proposed QT labelling. We reviewed the following materials:

- Sponsor's proposed label (NDA217388 / SDN 001; link);
- Previous IRT review report for IND 139521 dated 03/31/2022 in DARRTS (link);
- Investigator's brochure (IND 139521/SDN042; link); and
- Highlights of clinical pharmacology and cardiac safety (IND 139521/SDN042; Table 10 of "Request for waiver document", page 25. link).

1 Responses for the Sponsor

Question from the division: The review division is asking for our review and comments/ suggestions on the Applicant proposed labeling as follows.

(b) (4)

IRT's response: *Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.*

12.2 Pharmacodynamics Cardiac Electrophysiology At a dose 2.7 times the *maximum recommended dose for TRADENAME* (b) (4) (b) (4) *clinically significant QTc interval prolongation was not observed* (b) (4) (b) (4)
We propose to use labeling language for this product consistent with the draft FDA guidance, "QTc Information in Human Prescription Drug and Biological Product Labeling."

2 Internal Comments for the Division

- *None*

3 BACKGROUND

3.1 Product Information

Refer to previous QT evaluation report (link).

3.2 Sponsor's position related to the question

The Applicant proposed labeling as follows:

(b) (4)

3.3 Nonclinical Cardiac Safety

Refer to previous QT evaluation report (link).

3.4 Clinical Cardiac Safety

Refer to previous QT evaluation report (link).

3.5 Summary results of prior QTc assessments

Refer to previous QT evaluation report (link).

3.6 Relevant details of planned Phase 3 study

Not applicable.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

DONG GUO
05/05/2023 10:22:53 AM

ELIFORD N KITABI
05/05/2023 10:55:19 AM

CHRISTINE E GARNETT
05/05/2023 11:00:59 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 3/23/2023

TO: Division of Neurology I (DN I)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 217388

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) conducted an inspection for the site in May 2022. The inspection was conducted under the following submissions: NON-RESPONSIVE .

The following items were discussed with the site:

NON-RESPONSIVE

After review of the inspection findings, OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Clinical	BioPharma Services, Inc.	4000 Weston Road, Toronto, Ontario, Canada

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/s/

JAMES J LUMALCURI
03/23/2023 04:13:40 PM