NDA 217388

NDA APPROVAL

Ionis Pharmaceuticals, Inc.
Attention: Li Zhou, MS, RAC
Director, Regulatory Affairs
2855 Gazelle Court
Carlsbad, CA 92010

Dear Li Zhou:

Please refer to your new drug application (NDA) dated December 22, 2022, received December 22, 2022, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Wainua (eplontersen) injection.

This NDA provides for the use of Wainua (eplontersen) injection for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit the final printed container label that is identical to the container label submitted on November 2, 2023, and final printed carton labeling that is identical to the carton labeling submitted on December 18, 2023, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 217388**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Wainua (eplontersen) injection shall be 24 months months from the date of manufacture when stored at 2°C to 8°C.

ADVISORY COMMITTEE

Your application for Wainua was not referred to an FDA advisory committee because this drug is not the first in its class, the clinical trial design was acceptable, and evaluation of the safety data did not raise significant safety or efficacy issues that were unexpected for a drug of this class or in the intended population.

REQUIRED PEDIATRIC ASSESSMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from exposure to eplontersen during pregnancy; an unexpected serious risk of the potential presence of eplontersen in human breast milk; or an unexpected serious risk of carcinogenicity.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

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.

The timetable you submitted on October 13, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2024
Final Protocol Submission:	08/2025
Interim Study Report:	11/2026
	11/2027
	11/2028
	11/2029
	11/2030
	11/2031
	11/2032
	11/2033
	11/2034
	11/2035
Study Completion:	12/2035
Final Report Submission:	12/2036

4564-2 Perform a lactation study (milk only) in lactating women who have received a therapeutic dose of eplontersen using a validated assay to assess concentrations of eplontersen in breast milk.

The timetable you submitted on December 7, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2024
Final Protocol Submission: 07/2025
Study Completion: 12/2026
Final Report Submission: 05/2027

4564-3 Conduct a 26-week carcinogenicity study of eplontersen in Tg.rasH2 mouse.

The timetable you submitted on December 12, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 10/2021 (Submitted)
Final Protocol Submission: 01/2024
Study Completion: 04/2023
Final Report Submission: 05/2024

FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of atrioventricular block or to identify unexpected serious risks of glomerulonephritis and thrombocytopenia.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4564-4 Evaluate the incidence and provide analyses of glomerulonephritis, thrombocytopenia, and atrioventricular block observed in the placebo-

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

controlled study, ION-682884-CST, of eplontersen in adult hereditary and wild-type ATTR cardiomyopathy patients.

The timetable you submitted on October 13, 2023, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 08/2019 (Submitted)
Trial Completion: 11/2025
Final Report Submission: 10/2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 139521 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[8]

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for thrombocytopenia, serious bleeding with thrombocytopenia, glomerulonephritis and serious renal toxicity events, and ocular toxicity consistent with vitamin A deficiency. Include analyses of individual events as well as comprehensive summaries and analyses of these events as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with duration of eplontersen therapy, the time from first dose to adverse event onset, the time from last dose prior to the event onset, concomitant therapies, treatment given for the event, and outcome. Include analyses of the events by age. Include a comparison to background rates in the general population (overall and stratified by age), as well as background rates (if available) for patients with hereditary transthyretin amyloidosis (overall and stratified by age).

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[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[8] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[9].

If you have any questions, contact Justine Kankam, Regulatory Project Manager, at (301)-837-7650 or via email Justine.Kankam@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use

[9] https://www.uspnf.com/

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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