

NDA 218614

NDA APPROVAL

Ionis Pharmaceuticals, Inc.
Attention: Matt Buck, JD
Senior Vice President, Regulatory Affairs
2855 Gazelle Court
Carlsbad, CA 92010

Dear Matt Buck:

Please refer to your new drug application (NDA) dated and received April 19, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tryngolza (olezarsen) injection.

This NDA provides for the use of Tryngolza (olezarsen) injection as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS).

APPROVAL & LABELING

We have completed our review of this application, as amended. 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](http://www.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.

CARTON AND CONTAINER LABELING

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>.

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling 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 218614.**” 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 Tryngolza (olezarsen) injection shall be 36 months from the date of manufacture when stored under refrigerated condition at 2°C - 8°C (36°F to 46°F) in the commercial packaging.

ADVISORY COMMITTEE

Your application for Tryngolza was not referred to an FDA advisory committee because evaluation of the safety data when used in the treatment of FCS did not raise significant safety or efficacy issues that were unexpected for a drug of this class. In addition, there were no controversial issues that would benefit from advisory committee discussion.

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 assess a signal of a serious risk of chronic drug-induced liver injury.

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 this serious risk.

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 chronic drug-induced liver injury.

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

- 4760-1 Complete the ongoing randomized, double-blind, placebo-controlled trials (ISIS 678354-CS5 [CORE] and ISIS 678354-CS6 [CORE 2]) and the two-year open-label extension (OLE) trial (ISIS 678354-CS15) to evaluate the potential for drug induced liver injury with Tryngolza.

The timetable you submitted on December 16, 2024, states that you will conduct this trial according to the following schedule:

Interim Report Submission (ISIS 678354-CS5, ISIS 678354-CS6 trial data; OLE 678354-CS15 trial): June 2026

Interim Report Submission (OLE 678354-CS15 trial): June 2027

Interim Report Submission (OLE 678354-CS15 trial): June 2028

Trial Completion*: December 2028

Final Report Submission*: June 2029

*All three trials should be completed by the trial completion milestone and the final report submission should include data from all three trials.

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

Submit clinical protocol(s) to your IND 136692 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).

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.

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>.

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.

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*.⁴

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.⁵ Information and Instructions for completing the form can be found at FDA.gov.⁶

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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.⁷

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that for Tryngolza, you submit all serious and non-serious domestic and/or foreign cases of liver toxicity as 15-day “Alert reports” (described under 21 CFR 314.80(c)(1)), through the 5th year following initial United States approval.

⁴ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁷ <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>

We also request that you provide a narrative summary including analyses of events of liver toxicity as part of your required periodic safety reports (e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)), through the 5th year following initial United States approval.

Your analyses should include interval and cumulative data relative to the date of approval of Tryngolza. Your analyses should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, relevant laboratory values and diagnostic tests, concomitant therapies, confounders, underlying risk factors, treatment given for the event, drug disposition (e.g., dechallenge/rechallenge), and outcome at the time of the report (including whether the patient was hospitalized, experienced liver failure, liver transplant, or death).

To identify reports of liver toxicity, we request that you include the Standardised MedDRA Query (SMQ) Drug related hepatic disorders - comprehensive search (Broad) in your search.

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 website⁸.

⁸ <https://www.uspnf.com/>

If you have any questions, contact Ron Picking, Regulatory Project Manager, at 240-402-3211 or ronald.pickingiii@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, MD
Deputy Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

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

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/

LISA B YANOFF
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