CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218614Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 136692
Request Receipt Date	January 18, 2024 (SDN #138)
Product	Olezarsen (ISIS 678354)
Indication	Familial chylomicronemia syndrome
Drug Class/Mechanism of Action	apolipoprotein C-III antisense oligonucleotide
Sponsor	Ionis Pharmacueticals, Inc.
ODE/Division	OCHEN/DDLO
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	March 18, 2024

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

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

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

Olezarsen is intended to be an adjunct to diet to reduce triglycerides in patients with familial chylomicronemia syndrome (FCS).

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

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

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

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

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

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

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

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

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

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

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

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

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

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

Olezarsen (formerly ISIS 678354) is a GalNAc3 conjugated antisense oligonucleotide targeting and preventing apoC-III production. Apo-C-III is a key regulator of triglyceride (TG) metabolism via lipoprotein lipase dependent and

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

independent mechanisms. By reducing apoC-III production, olezarsen promotes TG clearance and lowers TG levels. The sponsor is pursuing an indication for olezarsen as an adjunct to diet for treatment of FCS. Due to reduced or absent lipoprotein lipase activity, individuals with FCS have persistent marked elevations in chylomicrons and triglycerides, which increases their risk of pancreatitis, the most serious, and potentially life-threatening consequence of this condition. The onset of symptoms in individuals with FCS usually occurs in childhood or adolescence, but the diagnosis may be delayed due to the rarity of the condition and varying severity of clinical presentation. Clinical signs include eruptive xanthomas, lipemia retinalis, and hepatosplenomegaly. Clinical symptoms include episodic, recurrent abdominal pain and fatigue.

Olezarsen shares the same nucleotide sequence as its parent drug, volanesorsen. Volanesorsen received a conditional marketing authorization for patients with FCS at high risk for pancreatitis by the European Medical Agency in 2019, but received a complete response letter from the Agency in 2018, (b) (4) .[1] Olezarsen is differentiated from volanesorsen by its conjugation to GalNaAc3, a ligand for the hepatocyte-specifc asialoglycoprotein receptor. The GalNac3 conjugate targets olezarsen to hepatocytes, its main site of action, which permits a different therapeutic dosing regimen of olezarsen (80 mg administered subcutaneously every 4 weeks) compared to volanesorsen (300 mg administered subcutanesously every week).

There are currently no FDA-approved drug therapies for FCS. Medications that are approved for the treatment of severe hypertriglyceridemia (TG ≥500 mg/dL) such as fenofibrates, prescription fish oil derivatives, and niacin are minimally effective in lowering TG in FCS patients. Management of FCS includes following an extremely restrictive low-fat diet and abstinence from alcohol, which is challenging for patients to maintain chronically.[2]

The IND for olezarsen was opened in January 2018, with a phase 2 trial of individuals with moderately elevated TG (TG 200 to 500 mg/dL) with established coronary artery disease. Following the primary analysis of the phase 2 trial, the sponsor elected to focus on the study populations of FCS and severe hypertriglyceridemia (TG ≥500 mg/dL). Multiple interactions between the sponsor and Division have occurred to discuss the sponsor's development plans for FCS including Type C meetings in July 2020 and August 2022; advice letters following review of phase 3 protocols, the statistical analysis plan (SAP), and the Integrated Summary of Safety (ISS), and a pre-NDA meeting in December 2023. Olezarsen received fast track designation in January 2023.

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

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

In support of the designation, the sponsor cites the results of the phase 3 trial, ISIS 678354-CS3, which evaluated the effect of olezarsen versus placebo on the percent change in TG at Month 6 (primary endpoint) and the adjudicated pancreatitis event rate at Week 53 (secondary endpoint).

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

The lipid biomarker, TG, has historically been accepted by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) as a surrogate for reduction in risk of pancreatitis and the basis of full approval for TG-lowering drugs in patients with severe hypertriglyceridemia (TG ≥500 mg/dL). Adjudicated pancreatitis would also be considered a clinically significant outcome measure in this patient population.

(b) (4)

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

None.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

The current mainstay for therapy for patients with FCS is a restrictive low-fat diet (<20 g fat). There are no FDA approved medications for the treatment of FCS. Classes of medications that are approved for the treatment of severe hypertriglyceridemia (TG≥500 mg/dL) related to other dyslipidemic conditions, and could be used off-label for the hypertriglyceridemia associated with FCS include fibrates, prescription fish oil derivatives, niacin, and statins. These medications are largely ineffective in lowering TG among patients with FCS, notably the lack of a treatment response has been proposed in some diagnostic algorithms to support further workup for FCS.[3]

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

No drugs developed for FCS have requested a breakthrough therapy designation.

11. Information related to the preliminary clinical evidence:

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

Although the olezarsen clinical development program intended to support the NDA for FCS comprises additional clinical studies, primarily phase 1, phase 2, and open-label extension studies, the clinical trial that best supports the breakthrough desgination request is trial ISIS 678354-CS3, which is described in the table below.

Table 1. Clincal Trial supporting the BTDR

Trial	Phase/Design	Treatment Groups	Key Efficacy Endpoints	Trial Results Placebo-subtracted
ISIS 678354-CS3	Phase 3, 53-week, randomized, double-blind, placebo-controlled	Adults with FCS (N=66) OLZ 80 mg SC Q4W (n=22) OLZ 50 mg SC Q4W (n=21) PBO SC Q4W (n=23)	Effect of olezarsen on the change from baseline in: • Percent change in TG (Month 6) • Adjudicated pancreatitis event rate (Week 53)	TG OLZ 80 mg: -44%; p=0.0009 OLZ 50 mg: -22%; p=0.0775 Pancreatitis OLZ 80 mg + 50 mg: -88%; event rate ratio 0.12 (p=0.0144)*
OLZ: Olezarsen; PBO: Placebo; SC subcutaneous; Q4W: every 4 weeks *nominal p-value				

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

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

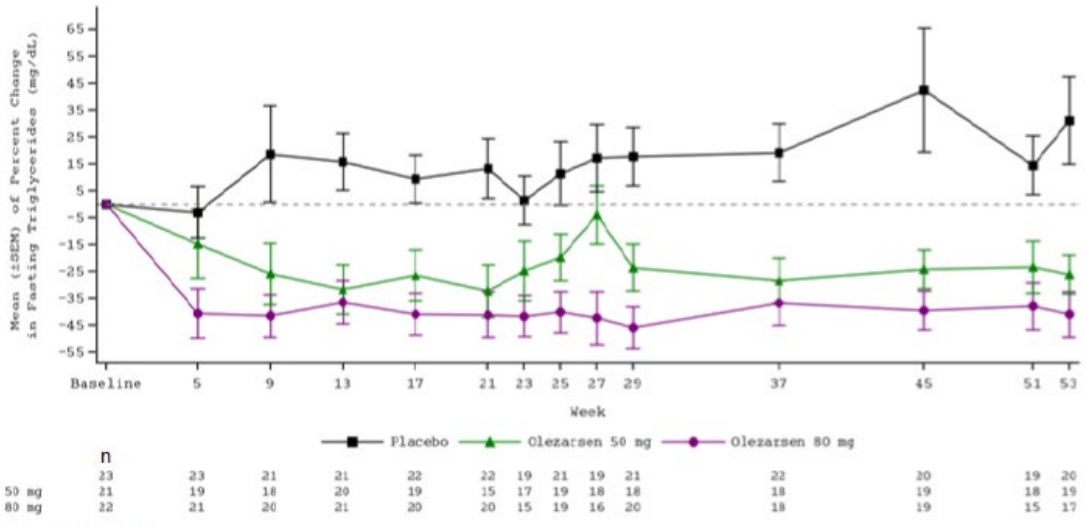
- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Trial ISIS 678354-CS3 was conducted to evaluate the efficacy and safety of olezarsen as compared to placebo in 66 adults with genetically confirmed FCS. The study was designed as a double-blind, placebo-controlled, 53-week study. Eligible study subjects were randomized to either olezarsen 50 mg, olezarsen 80 mg, or placebo administered subcutaneously every four weeks. The primary efficacy endpoint was percentage change in fasting TG from Baseline to Month 6 (average of Weeks 23, 25, 27 assessments).

A greater percent change in fasting TG levels from Baseline at 6 months was observed in the olezarsen 80 mg group compared with the pooled placebo group; placebo-adjusted 44% reduction for olezarsen 80 mg; p = 0.0009). A placebo-adjusted reduction (22%) in fasting TG levels from Baseline at 6 months was observed for patients treated with olezarsen 50 mg; however, the difference between fasting TG levels for patients treated with olezarsen 50 mg compared with placebo did not reach statistical significance (p = 0.0775) at 6 months (Table 1). Further review of the TG levels in the 50 mg cohort show a reduction of TG at all timepoints out to Week 53 with the exception of Week 27 (1 of the 3 timepoints average for the 6-month level), suggesting a clinical response to the 50 mg dose (Figure 1).



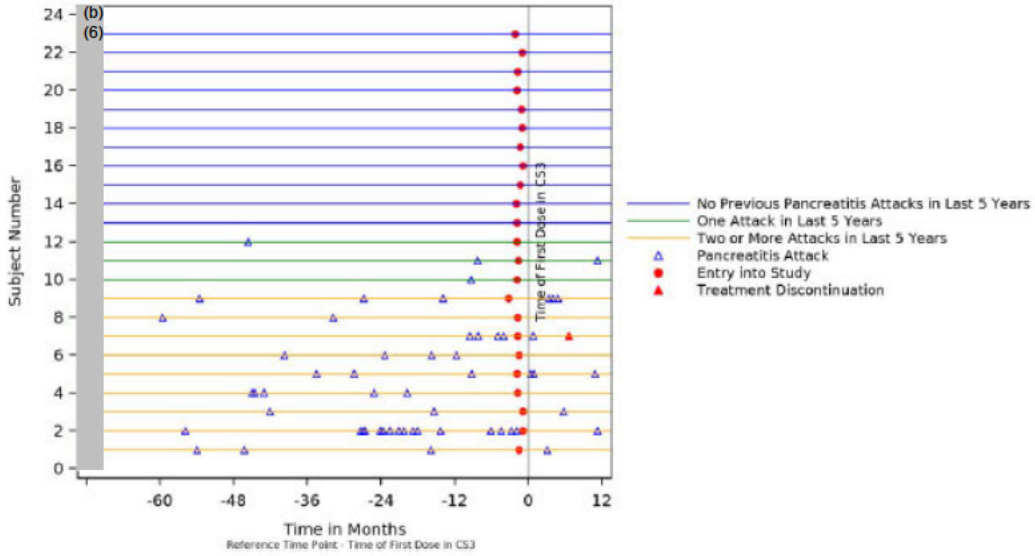
Source: Figure 14.2.1.5
Abbreviations: SEM = standard error of the mean

Figure 1. Study ISIS 678354-CS3: Triglyceride Levels Over Time – Mean (±SEM) Percent Change (Full Analysis Set)
Source: IND 136692, pre-NDA meeting background materials SDN 132

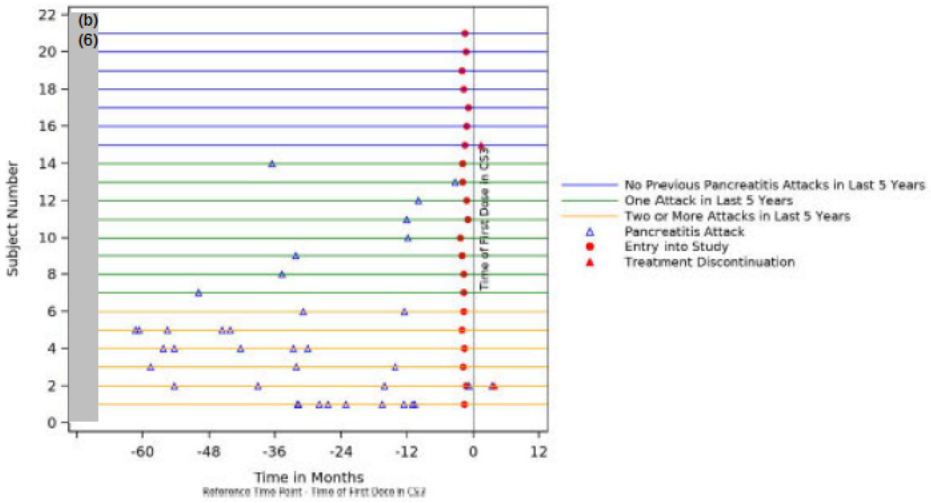
A decrease in TG is expected to reduce the risk of pancreatitis, although there is uncertainty regarding the magnitude of this risk reduction, given TG is a surrogate for this clinical outcome. As part of Trial ISIS 678354-CS3, acute pancreatitis event rate was an adjudicated secondary endpoint. The sponsor has provided preliminary results of the adjudicated pancreatitis event rate to support the clinical meaningfulness of TG reduction with olezarsen in the individuals with FCS

(Figure 2). During the treatment period, 1 subject experienced an adjudicated acute pancreatitis event in each of the olezarsen treatment groups (total 2 events) compared to 7 subjects with 11 events in the placebo group (mean pancreatitis event rate ratio 0.12 [nominal p-value 0.0144]. The majority of the pancreatitis events that occurred in this trial occurred in subjects that had more than 2 pancreatitis events in the 5 years prior to enrolling in this trial. Subjects without a history of pancreatitis in the last 5 years (blue line), did not experience an adjudicated pancreatitis event during the year long trial in any treatment group. The preliminary results, however, suggest a reduction in a clinical event of importance for this patient population (particularly in those at highest risk), and will be the subject of NDA review.

Placebo Group



50 mg Group



80 mg Group

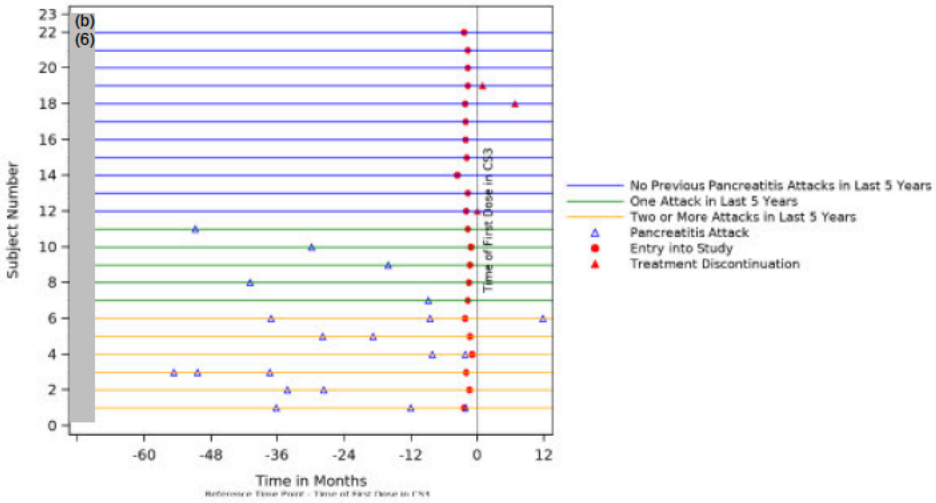


Figure 2. Adjudicated Pancreatitis Events by Treatment Group and Number of Adjudicated Pancreatitis Events in 5 Years Prior to Enrollment (Events Over Time by Subject; Full Analysis Set = 66)

As mentioned previously, volanesorsen, the parent drug of olezarsen, had a safety profile notable for severe thrombocytopenia. Other safety issues for volanesorsen included injection site reactions, hypersensitivity, imbalances in renal-related laboratory values and adverse events, and elevations in liver enzymes. These safety issues were closely monitored in the olezarsen clinical program. No subjects treated with olezarsen in trial ISIS 678354-CS3 had a platelet count below < 50,000/mm^3; 1 subject in the placebo group experienced platelet counts < 25,000/mm^3. No renal or hepatic safety signals were noted. Injection site reactions were low across all treatment groups. Overall, the incidence of treatment emergent adverse events in both the olezarsen 80 mg group (86.4%, n=19) and the olezarsen 50 mg group (85.7%, n=18) was lower compared with the placebo group (95.7%, n=22), primarily due to the higher number of gastrointestinal events reported in the placebo group. Three subjects treated with olezarsen discontinued study drug due to adverse events - one subject treated with olezarsen 50 mg died due to a serious treatment-emergent adverse event of sudden death (unknown cause), which was considered unrelated to olezarsen by the investigator and the sponsor, another discontinued due to consititutional symptoms (chills, myalgia, trismus), and one subject discontinued treatment due to chest discomfort, diarrhea, flushing, and vomiting.

The strengths of this clinical trial submitted to support a breakthrough designation request for olezarsen include permitting study subjects to enroll on stable background lipid lowering medication, inclusion of and enrichment for individuals with a history of pancreatitis, the study features of randomization, blinding, and inclusion of a placebo control in a rare disease population, adjudication of pancreatitis, use of multiple doses to assess an efficacy and safety dose response, and the longer term treatment duration to help assess safety of a drug intended for chronic use. As mentioned above, the 50 mg dose of olezarsen, did not achieve statistical significance at the pre-specified primary efficacy endpoint. (b) (4) .
However, the efficacy of the 80 mg dose of olezarsen on TG levels in this patient population is persuasive.

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

☒ GRANT:

Provide brief summary of rationale for granting:

FCS is a rare monogenic disorder of lipid metabolism characterized by excessive chylomicronemia and very severe hypertriglyceridemia. The most serious clinical consequence of this disorder is recurrent pancreatitis, which can be life-threatening. There is currently no approved product indicated for individuals with FCS. The treatment armamentarium would benefit from an effective and safe treatment option for this population. The statistically significant 44% reduction of TG with olezarsen 80 mg treatment, given the minimal effect of other TG lowering drugs in this population, is compelling. Reduction in TG levels is anticipated to reduce the risk for pancreatitis among individuals with hypertriglyceridemia. Preliminary reports suggest a nominally significant reduction in the acute adjudicated pancreatitis event rate with olezarsen treatment. In aggregate, the efficacy of olezarsen in conjunction with a generally well tolerated safety profile is preliminary clinical evidence of a substantial improvement over available therapies in this patient population.

☐ DENY:

Provide brief summary of rationale for denial:

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

The Division continues to engage with the sponsor of olezarsen – most recently in a pre-NDA meeting in December 2023. The sponsor has requested an orphan drug designation, which is under Agency review. The sponsor intends to submit a NDA for the FCS treatment indication in the second quarter of 2024. We have communicated to the sponsor that they may

request priority review as described in Guidance and that the decision on granting priority review will be based on the information and data available at the time the application is submitted.

14. List references, if any:

1. https://www.ema.europa.eu/en/medicines/human/EPAR/waylivra#ema-inpage-item-authorisation-details. Accessed 24 January 2024
2. Baass, A., Paquette, M., Bernard, S., Hegele, R. Familial chylomicronemia syndrome: an under-recognized cause of severe hypertriglyceridaemia. Journal of Internal Medicine; 2020, 287(4), 340–348.
3. Stroes E et al. Diagnostic algorithm for familial chylomicronemia syndrome. Atherosclerosis Supplements;2017;23:1-7

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

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

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

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

Revised 10/13/20 /M. Raggio

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/

MARY D ROBERTS
02/20/2024 01:59:23 PM

EILEEN M CRAIG
02/20/2024 02:41:31 PM

JOHN M SHARRETTS
02/20/2024 04:08:05 PM

IND 136692

MEETING PRELIMINARY COMMENTS

Ionis Pharmaceuticals
Attention: Stacy Woeppel
Director, Regulatory Affairs
2855 Gazelle Court
Carlsbad, CA 92010

Dear Stacy Woeppel:

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

We also refer to your September 27, 2023, correspondence, received September 27, 2023, requesting a meeting to discuss the content and format of a future new drug application (NDA) for the use of olezarsen for the treatment of familial chylomicronemia syndrome.

Our preliminary responses to your meeting questions are enclosed.

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

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at 240-402-3211.

Sincerely,

{See appended electronic signature page}

Ron Picking, Pharm.D.
Regulatory Project Manager
Diabetes, Lipid Disorders, and Obesity
Division of Regulatory Operations for Cardiology,
Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, December 12, 2023, 1:00 PM – 2:00 PM EST
Meeting Location: Video conference

Application Number: IND 136692
Product Name: olezarsen injection
Proposed Indication: Familial chylomicronemia syndrome (FCS)
Sponsor Name: Ionis Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Office of Cardiology, Hematology, Endocrinology, and Nephrology

Hylton V. Joffe, MD, MMSc	Director
Lisa B. Yanoff, MD	Deputy Director

Division of Diabetes, Lipid Disorders, and Obesity

John Sharretts, MD	Division Director
Eileen Craig, MD	Clinical Team Leader
Mary Roberts, MD	Clinical Reviewer

Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology

Li Li, PhD	Team Leader
Li Wang, PhD	Clinical Pharmacology Reviewer

Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology and Nephrology

David Carlson, PhD	Supervisory Toxicologist
Daniel Minck, PhD	Team Leader
Njwen Anyangwe, PhD	Nonclinical Reviewer

Office of Translational Sciences, Office of Biostatistics Division of Biometrics II

Feng Li, PhD	Team Leader
Kyunghee Song, PhD	Statistical Reviewer

Office of Pharmaceutical Quality, Office of New Drug Products, Division of New Drug Products III

Muthukumar Ramaswamy, PhD	Senior Pharmaceutical Quality Assessor

Office of Combination Products, OCPP, OC

Bindi Nikhar, MD, Associate Clinical Director

Office of Regulatory Operations, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology

Julie Van der Waag, MPH	Director, Project Management Staff
Elizabeth Solomon, MSHS	Chief, Project Management Staff
Ron Picking, PharmD	Regulatory Project Manager

SPONSOR ATTENDEES

Vickie Alexander, PhD	Executive Director, Clinical Development
Matt Buck, JD	Senior Vice President, Regulatory Affairs
Stacy Woeppel	Director, Regulatory Affairs
Richard Geary, PhD	Executive Vice President, Chief Development Officer
Scott Henry, PhD	Senior Vice President, Preclinical Development
Tae-Won Kim, PhD	Vice President, Toxicology Department
Ewa Prokopczuk, MD, PhD	Vice President, Cardiovascular Medicine
Jonathan Respress, PhD, MBA	Executive Director, TA Head- CardioMetabolism, Medical Affairs
Sam Tsimikas, MD	Senior Vice President, Global Cardiovascular Development
Xiang Gao, PhD	Vice President, Pharmacokinetics and Clinical Pharmacology
Rosie Yu, PhD	Executive Director, Pharmacokinetics and Clinical Pharmacology
Muneet Burke, MD	Executive Director, Drug Safety and Pharmacovigilance
Paul Wang, PharmD	Executive Director, Drug Safety and Pharmacovigilance
Charles Asare, MD	Vice President and Head of Drug Safety and Pharmacovigilance
Shuting Xia	Associate Director Biometrics
QingQing Yang	Executive Director Biometrics
Eric Bastings, MD	Senior Vice President, Development Strategy
Tracey Burr, PhD	Executive Director, CMC Regulatory Affairs
Asia Sikora Kessler, PhD	Director, Global Health Economics Outcome Research
Montserrat Vera Llonch	Executive Director, Global Health Economics Outcome Research

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Tuesday, December 12, 2023, 1:00 PM – 2:00 PM EST between Ionis Pharmaceuticals, Inc. and the Division of Diabetes, Lipid Disorders, and Obesity. We are sharing this material to promote a collaborative and successful discussion

at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Olezarsen is an N-acetyl galactosamine (GalNAc) conjugated antisense oligonucleotide (ASO) being studied for treatment of familial chylomicronemia syndrome (FCS) and severe hypertriglyceridemia (SHTG). Olezarsen is designed to target and degrade human apolipoprotein C-III messenger RNA, a key regulator of triglyceride (TG) metabolism. The nucleotide sequence of olezarsen is the same as that of volanesorsen (ISIS 304801), an unconjugated ASO previously under development for FCS. GalNAc conjugation is intended to provide similar efficacy to the unconjugated ASO at a lower and less frequent dose with fewer safety issues.

Completed trials of olezarsen include ISIS 678354-CS1, a phase 1 trial in otherwise healthy volunteers with elevated TG, AKCEA-CS1, a phase 1 trial in healthy Japanese volunteers, and ISIS 678354-CS2, a phase 2 trial in subjects with hypertriglyceridemia and established cardiovascular disease (CVD).

Ongoing trials consist of:

- ISIS 678354-CS3, a phase 3 trial in subjects with FCS (clinical study report (CSR) in progress)
- ISIS 678354-CS5 and ISIS 678354-CS6, phase 3 trials in subjects with SHTG
- ISIS 678354-CS8 and ISIS 678354-CS9, phase 2 trials in subjects with elevated TG and risk of CVD
- ISIS 678354-CS7, an open-label extension (OLE) of subjects previously treated with ISIS 304801
- ISIS 678354-CS13 and ISIS 678354-CS15, OLEs of CS3 and CS5, respectively and
- ISIS 678354-CS20, a bioequivalence study comparing vial and autoinjector (AI) Presentations (CSR in progress)

On September 27, 2023, the Sponsor submitted a Type B Pre-NDA meeting request to discuss a proposed new drug application (NDA) for treatment of FCS. (b) (4)

Results from a single adequate and well-controlled trial, CS3, with confirmatory evidence from trial CS8, are planned to be used to demonstrate efficacy. Safety data will be derived from trials CS2, CS3, CS7, CS8, and CS13.

Phase 3 trials evaluated doses of 50 mg and 80 mg every 4 weeks. The Sponsor proposes a recommended olezarsen dose of 80 mg once monthly.

The proposed commercial formulation is an autoinjector (AI) that the Sponsor has introduced, in place of a vial and syringe, in the ongoing open-label trials. Trial CS20 is intended to establish bioequivalence between the two presentations.

2.0 DISCUSSION

The questions from your background package are copied below in regular text. Our responses follow in **bolded** text.

2.1. Nonclinical

Question 1: Does the Agency agree that the overall nonclinical data package is adequate to support review of an NDA for olezarsen for the treatment of adults with FCS?

FDA Response to Question 1:
We agree that the nonclinical studies conducted with ISIS 678354, and supported by studies conducted with ISIS 304801, are consistent with those previously agreed upon with the Agency and appear appropriate in scope to support submission and review of an NDA for olezarsen.

We also remind you of the need to submit final study reports with the NDA, including reports for multiple nonclinical studies that have been indicated as completed or ongoing in previous documents submitted to us (e.g., background package submitted on April 27, 2023, and/or Annual Reports). The full list of reports was included in our June 7, 2023, Written Responses.

Additionally, in the list of nonclinical toxicology studies that will be included with the initial NDA submission, it is indicated that simplified trial summary (TS) files (ts.xpt files) will be submitted. The simplified TS files will only be accepted for those studies that were initiated prior to implementation of SEND data requirements for that particular type of study.[1]

2.2. Regulatory

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/study-data-technical-conformance-guide-technical-specifications-document

Question 2: Does the Agency agree that the body of evidence proposed to be included in the NDA is sufficient to inform an assessment of the benefit-risk profile for the proposed indication, i.e., as an adjunct to diet, for TG lowering (b) (4) in patients with familial chylomicronemia syndrome (FCS)?

FDA Response to Question 2:
You propose to demonstrate substantial evidence of effectiveness of olezarsen based on one adequate and well-controlled trial in individuals with FCS, trial CS3, and confirmatory mechanistic evidence from trial CS8, a randomized placebo-controlled trial in subjects without FCS but with elevated triglycerides with or without risk of cardiovascular disease.

To describe the safety profile of olezarsen, you propose to submit with the initial submission, the complete on-treatment and follow-up safety data from CS3, with the exception of post-treatment follow-up data from 6 subjects, all safety data up to the data cut-off (September 15, 2023) for CS8, safety data from the ongoing open-label trials in subjects with FCS from CS7 (data cut-off May 31, 2023), and CS13 (data cut-off August 5, 2023), and safety data from CS2 (phase 2 trial) and phase 1 trials. To evaluate the immunogenicity of olezarsen, the NDA will provide analyses of anti-drug antibody (ADA) positivity on pharmacokinetics (PKs), pharmacodynamics (PD), efficacy, and safety parameters of interest. You intend to establish bioequivalence between the vial and AI presentation of olezarsen from the results of trial CS20.

Using these trials, you calculate 157 subjects have been exposed to olezarsen (50 mg and 80 mg combined) for at least 12 months, and 215.9 total patient-years of olezarsen (50 mg and 80 mg) exposure. A total of 32 subjects in the open-label trial CS13 will have received 120 doses of the AI presentation of olezarsen with the initial NDA submission.

In general, this approach appears reasonable to support an NDA submission, however, we have the following items for you to consider.

- **Provide your rationale for the choice of May 31, 2023, for the data cut-off for the ongoing trial, CS7, versus a later cut-off date similar to the data cut-off point for CS13 (August 5, 2023).**
- **Provide additional details regarding the number and percentage of subjects that will have complete on-treatment and follow-up safety data from trial CS8 in the proposed initial NDA submission and safety updates.**

Ultimately, whether this data package is sufficient to inform the benefit-risk assessment to support the proposed indication will depend on the review of the results generated by the development program.

Question 3: Does the Agency agree that the proposed content of the NDA is a complete application?

FDA Response to Question 3:

You plan to provide the complete study reports with datasets in accordance with ICH guidance for industry E3 *Structure and Content of Clinical Study Reports*[2] recommendations for the individual trials, CS3 (final), CS8 (final), CS7 (interim), CS13 (interim), CS20 (final), CS2 (final), as well as the phase 1 trials, in Module 5 and summarize the efficacy data from the CS3 and CS8 individually within Module 2, Section 2.7.3. You plan to provide efficacy analyses from CS3 and CS8 only. No integrated summary of efficacy is planned given that a single trial of olezarsen, CS3, will provide efficacy data in subjects with FCS and that confirmatory evidence from trial ISIS 678354-CS8 was not conducted in the FCS population. Trial datasets will be provided in the study data tabulation model (SDTM) and analysis dataset model (ADaM) electronic format, including the integrated safety analysis datasets.

The integrated summary of safety (ISS) will consist of the individual study information from CS3 and CS8, and five safety data pools as described below.

- **Pool 1: Pivotal and confirmatory evidence: randomized, double-blind, placebo-controlled trials (CS3 + CS8)**

(b) (4)

- **Pool 4: All FCS population trials (CS3 + CS13 + CS7)**
- **Pool 5: All patient population trials (CS3 + CS13 + CS7 + CS2 + CS8)**

You intend for the ISS to be split between Module 2 and Module 5. The safety results from the individual trials as well as the pooled integrated summary of safety will reside in Module 2.7.4 (Clinical Summary of Safety). The integrated safety statistical tables and figures used to provide the source information for the ISS will reside in Module 5.3.5.3.

We disagree with the proposed content of the NDA. Interim descriptive efficacy analyses from the ongoing trials CS7 and CS13 at the time of the NDA reporting cutoff should be reported as part of the CSR and included in Module 5.3.5.2. Clarify that safety results from CS7 and CS13 will be included in the respective CSRs for these trials. Case report forms should be submitted for subjects reporting a fatal or non-fatal serious adverse events (SAEs), adverse events that resulted in discontinuation, and adverse events of special interest (AESIs). The safety results from the individual trials and the pooled integrated summary of safety including AESIs and other adverse events of interest should reside in Module 5.3.5.3 along with the statistical analysis plan, and analysis datasets supporting the ISS. A summary of the clinical safety may be provided in Module

[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.

2.7.4. Note that all tables and figures in any CSR or ISS should have the datasets and statistical codes provided for independent Agency replication.
Confirm that you intend to resubmit the finalized validation package for the anti-ISIS 678354 antibody binding assay as well as provide an Integrated Summary of Immunogenicity to be included in eCTD Module 5.3.5.3 as acknowledged in your July 23, 2021, response to our advice letter dated June 8, 2021, regarding the immunogenicity risk assessment of olezarsen.

Question 4: Does the Agency agree with the proposed plan for the safety update report required under 21 CFR 314.50(d)(5)(vi)(b)?

FDA Response to Question 4:
The following table outlines what you plan to include in the 90-day or 120-day safety update. A data cutoff of approximately 5 months prior to the 90-day submission date is proposed (December 1, 2023) and will include additional safety data from the trials CS3, CS8, CS13, and CS7. For trial CS3, the safety update will include 6 subjects with complete post-treatment follow-up safety data. We acknowledge that using a database lock date of December 31, 2023, for the 120-day safety update would provide only a small increase in subject exposure (1 to 2 more subjects) compared with the data cut-off for the 90-day safety update and therefore the December 1, 2023, cut-off is reasonable for the safety update.

Table 12: Additional Safety Data for the Safety Update

Study Number	Data to be Included in the 90- or 120--Day Safety Update
Phase 3 ISIS 678354-CS3: FCS patients	All follow-up data between the initial NDA and safety update reporting cutoffs
Phase 2b ISIS 678354-CS8: Triglycerides > 150 in patients with CVD risk	All follow-up data between the initial NDA and safety update reporting cutoffs
Phase 3 ISIS 678354-CS7: FCS patients previously treated with ISIS 304801 (volanesorsen)	All on-treatment and follow-up data between the initial NDA and safety update reporting cutoffs
Phase 3 ISIS 678354-CS13: FCS patients	All on-treatment and follow-up data between the initial NDA and safety update reporting cutoffs,

Note: Study data to be included in the initial NDA is listed in Table 7.
Abbreviations: CVD = cardiovascular disease FCS = Familial Chylomicronemia Syndrome; NDA = New Drug Application

For Trial CS3 the safety update will include 6 subjects with complete post-treatment follow-up safety data. For Trial CS8, confirm that at the initial NDA submission, complete on-treatment data and interim post-treatment follow-up safety data will be provided, and that with the safety update, complete post-treatment follow-up for all subjects will be provided. Provide the number of subjects and the duration of exposure at the initial NDA submission and at the 90-day or 120-day safety updates for the ongoing trials CS7 and CS13. Any SAEs, adverse events leading to discontinuation (DAEs), and AESI occurring after the data cut-off points but before the submission of the safety updates should also be provided. Narratives of SAEs, DAEs, or AESIs will need to be submitted as part of the safety update.

Question 5: Does the Agency agree that the olezarsen FCS NDA would qualify for a Priority Review?

FDA Response to Question 5:
You may request priority review as described in the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics.* The decision on whether priority review will be granted will be based on the information and data available at the time the application is submitted. If a priority review designation is granted for your application, you will be informed within 60 days of the receipt of the NDA.

Question 6: Does the Agency anticipate seeking guidance from an Advisory Committee?

FDA Response to Question 6:
We will need to conduct an initial review of the NDA to determine whether guidance from an Advisory Committee meeting for olezarsen is warranted. If your application is accepted for filing, the Filing Communication letter will provide our preliminary plans on whether we intend to hold an Advisory Committee meeting to discuss the application.

Question 7: Ionis proposes to provide the 24-month drug product stability data during the initial filing review period (within 60 days of NDA submission). Does the Agency agree with this proposal and that the submission of this data would not constitute a major amendment?

FDA Response to Question 7:
Your proposal to submit 24-month stability data within 60 days of NDA submission is reasonable.

FDA Additional Comments:

1. The following should be included in the initial NDA submission.
    a. In subjects treated previously with volanesorsen, provide the overall mean, median, and range of exposure of volanesorsen. Provide the mean, median, and range of time from the last volanesorsen treatment to enrollment in CS3 or CS7.
    b. Provide cumulative distribution curves to show the distribution of effect sizes in each treatment group for the primary endpoint at 6 months and at 1 year for trials CS3 and CS8.
    c. For all subjects with FCS, provide the genetic mutational analysis results confirming FCS.
    d. For each trial provide the following landmark dates: first subject screened, first subject dosed, last subject enrolled, last subject last dose, data cutoff date, and database lock date.

2. Complete the following tables for each trial and the safety pools. For all tables, show all treatment arms for each trial or pool, show the Risk Difference versus placebo for both 50 mg and 80 mg olezarsen doses. The FDA Medical Queries (FMQs) and the algorithm are described in the FMQ link below.

    https://downloads.regulations.gov/FDA-2022-N-1961-0001/attachment_1.xlsm

Table 1. Subjects with Adverse Events[1] for Dysglycemia-related FDA Medical Query (Narrow) and Preferred Term, Safety Population Pooled Analysis (or Trial X)[2]

FMQ (Narrow) Preferred Term	Drug Name Dosage X N=XXX n(%)	Drug Name Dosage Y N=XXX n(%)	Active Control N=XXX n(%)	Placebo N=XXX n(%)	Risk Difference (%) (95% CI)[3]
Hypoglycemia	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT1	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT2	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
Hyperglycemia	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT1	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT2	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
Diabetic Ketoacidosis	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT1	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT2	n(%)	n(%)	n(%)	n(%)	X (Y, Z)

Source: [include Source datasets and/or Software tools used].
Note: This table is based on Table 37 in the Integrated Guide
[1] Treatment-emergent AE defined as [definition]. MedDRA version X.
[2] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[3] Difference is shown between [treatment arms]. (e.g., Difference is shown between Drug Name Dosage X vs. Placebo
Abbreviations: FMQ, FDA Medical Query; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event.

Table 2. Subjects with Adverse Events[1] for Dysglycemia-related FDA Medical Query (Broad[2]) and Preferred Term, Safety Population, Pooled Analysis (or Trial X)[3]

FMQ (Broad) Preferred Term	Drug Name Dosage X N=XXX n(%)	Drug Name Dosage Y N=XXX n(%)	Active Control N=XXX n(%)	Placebo N=XXX n(%)	Risk Difference (%) (95% CI)[4]
Hypoglycemia	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT1	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT2	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
Hyperglycemia	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT1	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT2	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
Diabetic Ketoacidosis	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT1	n(%)	n(%)	n(%)	n(%)	X (Y, Z)
PT2	n(%)	n(%)	n(%)	n(%)	X (Y, Z)

Source: [include source and/or Software tools used].
Note: This table is based on Table 38 in the Integrated Guide
[1] Treatment-emergent AE defined as [definition]. MedDRA version X.
[2] Broad FMQ Analysis incorporates Narrow FMQ preferred terms to maximize sensitivity.
[3] Duration = [e.g., X week double-blind treatment period or median and a range indicating pooled trial durations].
[4] Difference is shown between [treatment arms]. (e.g., Difference is shown between Drug Name Dosage X vs. Placebo)
Abbreviations: FMQ, FDA Medical Query; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event.

Provide a table of the number and proportion of subjects in each trial and the safety pools meeting the following cut-offs post-baseline.

<u>Hypoglycemia</u>

- Level 1: Glucose 54 to <70 mg/dL
- Level 2: Glucose <54 mg/dL

<u>Hyperglycemia</u>

Fasting glucose

- Level 1: ≥100 to 125 mg/dL
- Level 2: ≥126 mg/dL or random glucose ≥200 mg/dL

HbA1c

- Level 1: ≥5.7% to <6.5%
- Level 2: ≥6.5%

Complete the table below for each trial and the safety pools.

Table 41. Patients With Hyperglycemia Algorithmic FMQ, Safety Population, Pooled Analysis (or Trial X)

Population Algorithmic FMQ Criterion	Drug Name Dosage X N = XXX n (%)	Placebo N = XXX n (%)	Risk Difference (%) (95% CI)[1]
Safety Population	**n(%)**	**n(%)**	
Patients with ≥ 1 Algorithmic Criterion	n(%)	n(%)	X (Y, Z)
Any Hyperglycemia FMQ Narrow Term	n(%)	n(%)	X (Y, Z)
Fasting Plasma Glucose ≥ 126 mg/dL	n(%)	n(%)	X (Y, Z)
≥2 Plasma Glucoses > 180 mg/dL	n(%)	n(%)	X (Y, Z)
Any New Diabetes Concomitant Medication	n(%)	n(%)	X (Y, Z)
Post Baseline HbA1c ≥6.5%	n(%)	n(%)	X (Y, Z)
HbA1c Increase ≥0.3% with Post Baseline HbA1c ≥5.7%	n(%)	n(%)	X (Y, Z)
Change from Baseline Fasting Plasma Glucose ≥ 20 mg/dL with Post Baseline Fasting Plasma Glucose > 100 mg/dL	n(%)	n(%)	X (Y, Z)
No History of Diabetes	**n(%)**	**n(%)**	
Patients with ≥ 1 Algorithmic Criterion	n(%)	n(%)	X (Y, Z)
Any Hyperglycemia FMQ Narrow term	n(%)	n(%)	X (Y, Z)
Fasting Plasma Glucose ≥ 126 mg/dL	n(%)	n(%)	X (Y, Z)
≥2 Plasma Glucoses >180 mg/dL	n(%)	n(%)	X (Y, Z)
Any New Diabetes Concomitant Medication	n(%)	n(%)	X (Y, Z)
Post Baseline HbA1c ≥6.5%	n(%)	n(%)	X (Y, Z)
HbA1c Increase ≥0.3% with Post Baseline HbA1c ≥5.7%	n(%)	n(%)	X (Y, Z)
Change from Baseline Fasting Plasma Glucose ≥ 20 mg/dL with Post Baseline Fasting Plasma Glucose > 100 mg/dL	n(%)	n(%)	X (Y, Z)
History of Diabetes	**n(%)**	**n(%)**	
Patients with ≥ 1 Algorithmic Criterion	n(%)	n(%)	X (Y, Z)
Any Hyperglycemia FMQ Narrow term	n(%)	n(%)	X (Y, Z)
Fasting Plasma Glucose ≥ 126 mg/dL	n(%)	n(%)	X (Y, Z)
≥2 Plasma Glucoses >180 mg/dL	n(%)	n(%)	X (Y, Z)
Any New Diabetes Concomitant Medication	n(%)	n(%)	X (Y, Z)
Post Baseline HbA1c ≥6.5%	n(%)	n(%)	X (Y, Z)
HbA1c Increase ≥0.3% with Post Baseline HbA1c ≥5.7%	n(%)	n(%)	X (Y, Z)
Change from Baseline Fasting Plasma Glucose ≥ 20 mg/dL with Post Baseline Fasting Plasma Glucose > 100 mg/dL	n(%)	n(%)	X (Y, Z)

Source: [include Applicant source, datasets and/or software tools used].
[1] Difference is shown between [treatment arms]. (e.g., difference is shown between Drug Name dosage X vs. placebo).
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; N, number of patients in treatment arm; n, number of patients with adverse event

Provide a table of the number and proportion of subjects meeting the following cut-offs (with the exception of platelets) post baseline for each trial and the safety pools.

Table 61. Abnormality Level Criteria[1] for Hematology Laboratory Results

Parameter	Level 1	Level 2	Level 3
Complete Blood Count			
WBC, low (cells/µL)	<3500	<3000	<1000
WBC, high (cells/µL)	>10,800	>13,000	>15,000
Hemoglobin, decrease (g/dL)	N/A	>1.5 dec. from baseline	>2 dec. from baseline
Hemoglobin, increase (g/dL)	N/A	>2 inc. from baseline	>3 inc. from baseline
Platelets, low (cells/µL)	<140,000	<125,000	<100,000
Hemoglobin, male (g/dL)	12.5-13.5	<12.5	<10.5
Hemoglobin, female (g/dL)	11.0 – 12.0	<11	<9.5
WBC Differential			
Lymphocytes, low (cells/µL)	<1000	<750	<500
Lymphocytes, high (cells/µL)	>4000	>10000	>20000
Neutrophils, low (cells/µL)	<2000	<1000	<500
Eosinophils, high (cells/µL)	>650	>1500	>5000
Coagulation Studies			
PT, increase (sec)	>1.1 x ULN	>1.3 x ULN	>1.5 x ULN
PTT, increase (sec)	>1.0 x ULN	>1.21 x ULN	>1.41 x ULN

[1] Provided for the purpose of identifying outliers.
Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cell; ULN, Upper Limit of Normal

3. Refer to combination product comments provided in the Written Responses Only meeting dated February 16, 2022.

4. Form 356h - In your future submissions, the Form FDA 356h should identify your product as a combination product (see form field 24). Also, identify all facilities involved in the manufacturing of the combination product, including all facilities

involved in the manufacturing of each constituent part and all facilities responsible for the disposition (e.g., release) of the combination product.

5. Part 3 combination products are subject to post-market reporting safety requirements per 21 CFR Part 4.B. For more information on post-market safety reporting requirements for combination products, see the Postmarketing Safety Reporting for Combination Products website[3].

6. Prepare and submit individual clinical study datasets to facilitate evaluating the impact of immunogenicity (formation of ADA to your product) on the PKs of your product. Relevant datasets for the evaluation of immunogenicity impact include the ADaM datasets (i.e., ADIS, ADPC, ADSL) which are to be derived from the SDTM datasets (i.e., IS, PC, DM). Refer to individual sections below for necessary variables.

   All datasets are to follow the CDISC standards described in the current version of SDTM and ADaM implementation guide[4]. The ADIS dataset is based on the Analysis Data Model (ADaM) Basic Data Structure (BDS) and derived from Immunogenicity Specimen Assessments (IS) domain described in the SDTMIG v3.4 of CDISC. Also refer to the FDA's guidance for industry *Providing Regulatory Submissions In Electronic Format —Standardized Study Data* and the FDA's guidance for industry *Study Data Technical Conformance Guide*.

   a. Analysis Dataset for Immunogenicity Specimen (ADIS):
      This is a one record per subject per parameter per time point dataset that contains a comprehensive set of variables pertaining to the subject and their qualitative ADAs measures. Each test type for ISTEST variable in IS dataset should be represented under PARAM variable in the ADIS dataset. Example test types for ISTEST in IS dataset are screen, confirm, titer test, and neutralizing antibodies (nAb) test, and nAb titer test. The corresponding PARAM variables in ADIS dataset are screen, confirm, and titer results for ADA, nAb and nAb titer, respectively. A derived variable "ADA Conclusion" is to be used to represent the combined results of screen test and confirm test for ADA test. Titer results should account for the minimum required dilution (MRD) and take a numerical result without any transformation. For example, a sample with ADA confirmed positive that became negative after the first dilution in titer assay would report a titer value of MRD and a sample with ADA confirmed positive and became negative after the second dilution in titer assay would report a titer value of MRD multiplied by the dilution factor. See Table 1 for an example.

[3] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products
[4] https://www.cdisc.org/standards/foundational/sdtmig/sdtmig-v3-4

Table 1. Example of required analysis variable in ADIS dataset and corresponding variable names in IS domain

Variable names in IS domain									
STUDYID	**USUBJID**	**ISTEST**	**VISIT**	**VISITNUM**	**ISSCAT**	**ISSTRESC**	**ISSTRESN**	**TRTP**	**ISSLLOQ**
Variable names in ADIS dataset									
STUDY ID	**USUBJ ID**	**PARAM**	**AVISIT**	**AVISITN**	**PARCAT1**	**AVALC**	**AVAL**	**TRTP**	**ISSLLOQ**
ABC-01	123456	Screening	Visit 1	1	Immunogenicity	Positive		200 mg drug A	
ABC-01	123456	Confirm	Visit 1	1	Immunogenicity	Positive		200 mg drug A	
ABC-01	123456	*ADA Conclusion	Visit 1	1	Immunogenicity	Positive		200 mg drug A	
ABC-01	123456	ADA Titer	Visit 1	1	Immunogenicity	MRD x dilution factor		200 mg drug A	1
ABC-01	123456	nAb	Visit 1	1	Immunogenicity	Negative	1	200 mg drug A	
ABC-01	123456	nAb Titer	Visit 1	1	Immunogenicity	MRD x dilution factor	1	200 mg drug A	

* Report ADA Conclusion test results as following: AVALC = Negative when (i) the Screen result = Negative or (ii) Screen result = Positive and Confirm result = Negative. AVALC = Positive when Confirm result = Positive

b. Analysis Dataset for Pharmacokinetic Concentrations (ADPC):
This is a one record per subject per PK concentration per time point dataset that contains a comprehensive set of variables pertaining to the subject and their quantitative PK measures**.** See Table 2 for an example.

Table 2. Example of required analysis variable in ADPC dataset and corresponding variable names in PC domain

Variable names in PC domain								
STUDYID	**USUBJID**	**PCTEST**	**VISIT**	**VISITNUM**	**PCCAT**	**PCSTRESC**	**PCSTRESN**	**PCLLOQ**
Variable names in ADPC dataset								
STUDYID	USUBJID	PARAM	AVISIT	AVISITN	PCCAT	AVALC	AVAL	-
ABC-01	123456	Drug A	Visit 1	1	Analyte	<2		2
ABC-01	123456	Drug A	Visit 1	1	Analyte	100	100	2
Variable names in PC domain (continued)								
PCTPT	PCTPTNUM	PCSTRESU	PCDY	PCSPEC	PCMETHOD	PCTESTCD	TRTP	
Variable names in ADPC dataset (continued)								
PCTPT	PCTPTNUM	PCSTRESU	ADY	PCSPEC	PCMETHOD	PARAMCD	TRTP	
Pre-dose	1	ng/mL	1	serum	ELISA	A	200 mg drug A	
Post-dose	2	ng/mL	1	serum	ELISA	A	200 mg drug A	

c. Analysis Dataset Subject Level (ADSL):
This is a one record per subject dataset that contains variables such as subject-level population flags, planned and actual treatments for each period, demographic information, stratification and subgrouping variables, important dates, and so forth. See Table 3 for an example.

Table 3. Example of required analysis variable in ADSL dataset and corresponding variable names in DM domain

Variable names in DM domain								
STUDYID	**USUBJID**	**ARM**	**ARMCD**	**TRTP**	**RFSTDTC**	**RFENDTC**	**RFXSTDTC**	**RFXENDTC**
Variable names in ADSL domain								
STUDYID	**USUBJID**	**ARM**	**ARMCD**	**TRTP**	**RFSTDTC**	**RFENDTC**	**RFXSTDTC**	**RFXENDTC**
ABC-01	123456	Drug A	A	200 mg drug A	2006-01-12	2006-03-10	2006-01-12	2006-03-10

Variable names in DM domain (continued)								
RFICDTC	**RFPENDTC**							
Variables names in ADSL domain (continued)								
RFICDTC	**RFPENDTC**							
2006-01-15	2006-04-01							

d. Consistency in variable nomenclature between ADIS, ADPC, and ADSL
To facilitate the creation of an analysis dataset from ADIS, ADPC, and ADSL, data variables in these datasets should be named consistently. For example, common data variables include, but not limited to, STUDYID, USUBJID, TRTP.

7. Complete the bioanalytical method performance summary of PK and PD as recommended in FDA guidance for industry Technical Specifications Document entitled *Bioanalytical Methods Templates*.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our October 16, 2023, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under

PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[5]

4.0 PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content*

[5] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans.[6] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[7]

We acknowledge you are seeking orphan drug designation for your proposed indication for the treatment of FCS. If your drug product receives orphan drug designation for this indication, you would be exempt from these requirements.

5.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[8] and Pregnancy and Lactation Labeling Final Rule[9] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant

[6] https://www.fda.gov/media/86340/download
[7] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[8] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[9] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

6.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[10] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[11]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

7.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[12]

[10] https://www.fda.gov/media/84223/download
[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[12] https://www.fda.gov/media/85061/download

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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