CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219407Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 142564

MEETING PRELIMINARY COMMENTS

Ionis Pharmaceuticals, Inc.
Attention: Nancy Johansen
Executive Director, Global Regulatory Affairs
2855 Gazelle Court
Carlsbad, CA 92010

Dear Nancy Johansen:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for donidalorsen (ISIS 721744).

We also refer to your February 6, 2024, correspondence requesting a virtual Pre-NDA meeting to receive feedback regarding the content and format to support a marketing application for donidalorsen (ISIS 721744) for prophylaxis to prevent attacks of HAE in patients 12 years of age and older.

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 (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

[1] 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.

ENCLOSURE:

Meeting Preliminary Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 15, 2024
Meeting Location: Videoconference

Application Number: IND 142564

Product Name: donidalorsen (ISIS 721744)
Indication: Hereditary Angioedema

Sponsor Name: Ionis Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1)

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 April 15, 2024, from noon to 1PM EST via Videoconference between Ionis Pharmaceuticals and the Division of Pulmonary, Allergy, and Critical Care. 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

Ionis Pharmaceuticals, Inc. (Ionis) submitted a Type B meeting request on February 6, 2024, to discuss the content and format to support a marketing application for donidalorsen (ISIS 721744) for prophylaxis to prevent attacks of HAE in patients 12 years of age and older. The Division granted the meeting on February 20, 2024. Ionis submitted the briefing package on March 6, 2024. The expected outcome of the meeting is to clarify questions outlined in the briefing package.

2.0 DISCUSSION

Nonclinical

Question 1
Consistent with the advice received at the End of Phase 2 meeting, Ionis has completed a 27-weekTg.rasH2 mouse carcinogenicity study for donidalorsen, and the final report will be submitted with the marketing application. The 2-year rat carcinogenicity study is currently in progress (> 1-year treatment), but based on projected filing timelines, these data will not be available at submission. It is the Sponsor's intent to submit a summary of the in-life data (mortality, body weight and clinical signs) on the 2-year rat study that are available at the time of submission and to submit the final report as a post marketing commitment. Does the Agency agree with this approach?

FDA Response to Question 1:
Yes, we agree. The final report for the 27-week Tg.rasH2 mouse carcinogenicity study should be available at the time of the NDA submission. It would be acceptable to submit a summary of the in-life data for the 2-year carcinogenicity study in rats at the time of the NDA submission and to submit the final report as a post marketing requirement (PMR).

Question 2
Does the Agency agree that the nonclinical data package is adequate to support the review of an NDA for donidalorsen as a prophylaxis to prevent attacks of HAE in patients 12 years of age and older?

FDA Response to Question 2:
Pending review, the nonclinical data package with donidalorsen appear acceptable to support an NDA filing for the proposed indication.

Clinical

Question 3
Does the Agency agree that the clinical data package is adequate to support a new drug application for the proposed indication?

FDA Response to Question 3:
We agree that the proposed clinical data package appears acceptable to support review of the NDA, pending review of the application contents once submitted.

Question 4
Does the Agency agree that BIMO listings will be included only for the studies that are used to support safety and efficacy claims for the proposed indication (i.e., ISIS 721744-CS2 and ISIS 721744-CS5)?

FDA Response to Question 4:
Yes, we agree.

Question 5
Does the Agency agree the body of evidence proposed to be included in the NDA, and the proposed structure and content of the proposed NDA is sufficient constitute a complete application?

FDA Response to Question 5:

1. Your NDA proposal does not specify the autoinjector device information you plan to submit, so we refer you to the FDA Written Responses issued on February 3, 2023, regarding the requested NDA contents for the autoinjector configuration.

2. We refer you to Type B End of Phase 2 Meeting Minutes issued on October 18, 2021, regarding the assessment of effect of hepatic impairment on the hepatic uptake/accumulation/metabolism/elimination of ISIS 721744 and its metabolites. The impact of hepatic impairment on the PK and PD of your proposed product will be a review issue. Your proposed labeling should reflect the available data regarding assessment of hepatic and renal function impact on ISIS 721744 and its metabolites.

3. We acknowledge that the systemic exposure of shortmer metabolites of ISIS 721744 is generally low in your clinical program. Provide general justifications of how antisense oligonucleotides are metabolized and eliminated in the human body. Provide a table summarizing all the non-endogenous nucleotide modifications of ISIS 721744 and justify whether any FDA approved nucleotide drug products contain those modifications at NDA submission.

4. We are reviewing your proposed PRO evidence dossier. If we have comments related to this, we will issue them in a follow-up advice letter at a later time.

Question 6
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 6:
Yes, we agree.

Question 7
Does the Agency anticipate seeking guidance from an Advisory Committee?

FDA Response to Question 7:
We do not currently anticipate convening an Advisory Committee meeting, although this will depend on efficacy or safety concerns identified during the NDA review.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 20, 2024, 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.[2]

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

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

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 draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[3] 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.[4]

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. 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.

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*.[7]

SUBMISSIONS WITH REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[8] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

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[5] https://www.fda.gov/media/84223/download

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

[7] https://www.fda.gov/media/85061/download

[8] https://www.fda.gov/media/124795/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/

COLETTE C JACKSON
04/10/2024 04:29:54 PM

IND 142564

MEETING MINUTES

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

Attention: Matthew Rael, MS
Associate Director, Regulatory Affairs

Dear Mr. Rael:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ISIS 721744.

We also refer to the teleconference meeting between representatives of your firm and the FDA on August 30, 2021. The purpose of the meeting was to discuss the adequacy of the existing and proposed nonclinical and clinical development package to support a marketing application for ISIS 721744 for prophylaxis to prevent attacks of HAE in patients 12 years of age and older.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: August 30, 2021, from noon to 1 PM EST
Meeting Location: via teleconference

Application Number: IND 142564
Product Name: ISIS 721744

Indication: Prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 years and older.

Sponsor Name: Ionis Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1)

Meeting Chair: Sally Seymour, M.D.
Meeting Recorder: Colette Jackson

FDA ATTENDEES

Division of Pulmonology, Allergy, and Critical Care
Sally Seymour, M.D., Division Director
Kelly Stone, M.D., Associate Director for Therapeutic Review
Rachel Bean, M.D., Clinical Reviewer
Colette Jackson, Senior Regulatory Health Project Manager

Division of Pharmacology/Toxicology for Immunology and Inflammation (DPT-II)
Eleni Salicru, Ph.D., Pharmacology/Toxicology Reviewer
Andrew Goodwin, Ph.D., Pharmacology/Toxicology Supervisor

Office of Pharmaceutical Quality
Craig Bertha, Ph.D., Product Quality Reviewer

Office of Clinical Pharmacology
Qianni Wu, Ph.D., Clinical Pharmacology Reviewer
Yunzhao Ren, Ph.D., Clinical Pharmacology Team Leader
Hobart Rogers, Ph.D., Reviewer, Translational and Precision Medicine

Office of Biostatistics
Mingyu Xi, Ph.D., Statistical Reviewer
Yongman Kim, Ph.D., Statistical Team Leader

Office of Surveillance and Epidemiology, Division of Mediation Errors and Prevention Analysis
Lissa Owens, Pharm.D., Safety Evaluator
Tamika White, Senior Regulatory Health Project Manager

SPONSOR ATTENDEES
Richard Geary, Ph.D., Executive Vice President, Development
Eugene Schneider, M.D., Executive Vice President, Chief Clinical Development Officer
Charles Asare, M.D., MPH, Vice President and Head of Drug Safety
Kenneth Newman, M.D., MBA, Vice President, Clinical Development
Scott Henry, Ph.D., Vice President, Preclinical Development
Vickie Alexander, Ph.D., Executive Director, Clinical Development
Yanfeng Wang, Ph.D., Executive Director, Pharmacokinetics and Clinical Pharmacology
Montserrat Vera-Llonch, M.D., MPH, MSc, Senior Director, Global Health Economics & Outcomes
Lijiang (LJ) Shen, M.D., Ph.D., Director, Preclinical Development
Laura Bordone, Ph.D., Associate Director, Clinical Development
Charvi Nanavati, Ph.D., Associate Director, Pharmacokinetics
Matt Buck, JD, Vice President, Regulatory Affairs
Matthew Rael, MS, Director, Regulatory Affairs
Nancy Johansen, Director, Regulatory Affairs

1.0 BACKGROUND

Ionis Pharmaceuticals, Inc. (Ionis) submitted a Type B meeting request on May 14, 2021, to discuss the adequacy of the existing and proposed nonclinical and clinical development package to support a marketing application for ISIS 721744 for prophylaxis to prevent attacks of HAE in patients 12 years of age and older. The Division granted the meeting on June 8, 2021. Ionis submitted the briefing package on June 29, 2021. The expected outcome of the meeting is to clarify questions outlined in the briefing package. The FDA sent Preliminary Comments to Ionis on August 26, 2021. On August 27, 2021, Ionis sent a slide deck with discussion points for the meeting via email and was submitted officially to the IND on September 8, 2021. The slide deck is included in these meeting minutes under Section 6.0 Attachments and Handouts.

2.0 DISCUSSION

Pharmacology/Toxicology

Question 1
Does the Agency agree that the proposed nonclinical development program is adequate to support initiation of the Phase 3 study and a New Drug Application for ISIS 721744 for prophylaxis of HAE attacks in patients 12 years of age and older?

FDA Response:
No, we do not agree. Additional nonclinical studies are needed to support initiation of the proposed phase 3 study and a New Drug Application for ISIS 721744, as discussed below.

We note that there is limited nonclinical evaluation of the metabolism of ISIS 721744 and its THA linker. The publication by Shemesh et al., (Molecular Therapy - Nucleic Acids (2016) 5, e319; doi:10.1038/mtna.2016.31) describing the metabolism of ION-681257 is supportive; however, prior to the start of phase 3 clinical studies, provide data that characterize the metabolism of ISIS 721744 and its THA linker through literature (your work and/or non-proprietary literature) and actual metabolism studies in monkey and mouse (as needed) to demonstrate reasonable comparability to human metabolism. See also responses to Questions 3 and 4.

You plan to conduct a 6-month carcinogenicity study in rasH2 transgenic mice and to seek a waiver for a 2-year rat carcinogenicity study for ISIS 721744. We acknowledge the rationale provided in the meeting package for seeking a waiver for a 2-year rat carcinogenicity study; however, based on input from the Executive Carcinogenicity Assessment Committee (ECAC) of CDER, the conduct for a 2-year carcinogenicity study in rats cannot be waived. As such, we recommend that the protocols for the 6-month carcinogenicity study in rasH2 transgenic mice and the 2-year rat carcinogenicity study and supporting dose range-finding studies be submitted for evaluation by the ECAC of CDER. Final carcinogenicity study reports should be available with the NDA. Refer to the ICH M3(R2), S1A, S1B, and S1C Guidance documents for further information.

***Additional Nonclinical Comment**:*

1. *Prior to the start of phase 3 clinical trials, provide a toxicologic assessment for findings of liver inflammation and necrosis observed in female mice at doses ≥1 mg/kg from the 26-week study (Sponsor Reference #721744-AS04). These findings were not observed in the concurrent control group and appear to be clear response to drug treatment despite the lack of a dose-response relationship. We acknowledge that these findings were confined to males at 12 mg/kg.*

Discussion for FDA Response to Question 1:
Ionis opened the discussion referring to Slide #6 of their slide deck which outlines their position that the existing data for ISIS 721744 (b) (4) adequate to initiate Phase 3 trials. GalNAc trishexylamino (THA) linker metabolism is well understood and consistent across species. The FDA noted that the information provided in the slide deck is new information not included in the briefing package. The new data provided could address the Agency's concerns regarding the THA linker metabolism, but more information will need to be submitted to the IND for review prior to the initiation of the Phase 3 trials. The FDA asked Ionis to clarify if the PK profiles and Clinical Pharmacology information of the other THA linker compounds outlined in slide #7 have

been submitted to the Agency. Ionis stated that they have partnered with another company to qualify the metabolism across the different compounds and will reach out to them to provide the clinical PK study report to IND 142564 prior to initiation of their phase 3 trials.

The FDA asked Ionis if patients with mild to moderate renal impairment will be included in their phase 3 studies and if a dedicated hepatic impairment study is planned. Ionis stated they intend to include patients with mild to moderate renal impairment in their phase 3 studies. In addition, Ionis proposes to include mild hepatic impairment subjects in the phase 3 studies and conduct a dedicated hepatic impairment study in subjects with moderate to severe hepatic impairment, though the hepatic impairment study may be conducted as a post-marketing study.

Ionis intends to submit a toxicological assessment of the liver findings from the 26-week toxicity study in mice prior to initiation of the phase 3 trials.

The FDA stated it would be helpful to have the assessments of THA linkers (with similarities/differences) across antisense oligonucleotide programs to better understand the metabolism and requested that Ionis submit this information to IND 142564 for review. Ionis stated they will submit this information to the IND ahead of the phase 3 trials.

Question 2
Does the Agency agree to a waiver from the requirement to conduct an embryo-fetal development study of ISIS 721744 in rabbits?

FDA Response:
Pending review of the available, ongoing, and planned reproductive and developmental toxicity studies with ISIS 721744 and ISIS 546254 (and the mouse surrogates ISIS 722059 and ISIS 482584), we agree that an embryo-fetal development study of ISIS 721744 in rabbits is not needed.

Refer to the ICH M3(R2) Guidance regarding the timing of reproductive toxicology studies and the inclusion of women of childbearing potential in clinical studies.

The ongoing fertility and early embryonic development toxicity study in CD-1 mice should be available prior to the initiation of the phase 3 clinical trials with ISIS 721744. The planned pre and postnatal development study in CD-1 mice can be conducted in parallel with phase 3 trials and provided with a potential NDA.

Discussion for FDA Response to Question 2:
There was no discussion held for FDA Response to Question 2.

Clinical Pharmacology

Question 3

Does the Agency agree that the clinical pharmacology program is adequate to support initiation of the Phase 3 study and a New Drug Application of ISIS 721744 for prophylaxis to prevent attacks of HAE in patients 12 years of age and older?

FDA Response:

Based on the provided information, ISIS 721744 can be taken up by and enriched in hepatocytes, followed by metabolism via non-CYP enzymes. In addition, it appears that the trishexylamino (THA) linker and its metabolites were mainly excreted in the biliary system in animal studies. Although you provided some justifications, the effect of hepatic impairment on the uptake, distribution, accumulation, and metabolism of ISIS 721744 and the THA linker in the liver remains a concern. It is unclear if systemic exposure of ISIS 721744 will reflect the change of the accumulation and metabolism of ISIS 721744 and the THA linker in the liver. Although you may conduct population PK analyses to assess the hepatic impairment, the results may have limited interpretations. Therefore, we recommend that you include patients with mild to moderate hepatic impairment (based on the Child-Pugh system) in your phase 3 study CS5 and carefully monitor the liver function tests and related symptoms in these patients to provide safety information to evaluate the liver toxicity. In addition, the inclusion of these patients will help in assessing the systemic exposure of ISIS 721744 in patients with hepatic impairment via population PK analysis.

We also recommend that you include patients with renal impairment with an appropriate eGFR cutoff in the proposed CS5 study to support the population PK analysis.

A further investigation will be required if any significant PK/safety findings related to hepatic/renal impairment are identified in your clinical program.

It appears that your justification for the waiver of clinical DDI studies was mainly based on the active metabolite, i.e., the antisense oligonucleotide. We notice that the DDI potential of the THA linker and its major metabolites have not been evaluated in your clinical program. As ISIS 721744 is mainly taken up by the hepatocytes and undergoes metabolism to release the THA linker, the concentration of THA in hepatocytes is expected to be considerably higher than the systemic exposure. Therefore, we recommend that you assess the DDI potential of the THA linker and/or its major metabolites in vitro on the common CYP enzymes and transporters. This information will be used to justify the needs for clinical DDI studies. For details, refer to the FDA final guidance (2020): "In Vitro Drug Interaction Studies -- Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions".
https://www.fda.gov/media/134582/download

In addition, we recommend that you use the final to-be-marketed drug product in the proposed pivotal phase 3 trials. If you intend to change drug product (such as changing a prefilled syringe to an autoinjector) after the phase 3 trial, we expect a dedicated relative BA study to be conducted to bridge the prefilled syringe and the autoinjector.

For the characterization of QT prolongation risk, currently we treat oligonucleotides similar to that of small molecules. Based on the submitted data, it appears that the risk of QT prolongation associated with subcutaneous administration of ISIS-721744 could be characterized using an integrated nonclinical safety assessment conducted according to best practices (ICH S7b Q&A 1.1 and 1.2) in conjunction with clinical study (Study # ISIS 721744- CS1). In general, we suggest conducting an integrated nonclinical safety assessment (ICH E14 Q&A 5.1), if sufficiently high multiples of the clinical exposure, to waive the inclusion of a separate positive control, were not obtained in clinical QTc risk assessment. Whether an integrated nonclinical safety assessment conducted according to best practices is adequate as a substitute for a thorough QT study is a review issue.

Discussion for FDA Response to Question 3:
There was no discussion held for FDA Response to Question 3.

Question 4
Does the Agency agree to waive the requirement for a clinical ADME study of ISIS 721744?

FDA Response:
No, we do not agree. It appears that in Study CS1, you focused on the metabolite profiling of anti-sense oligo (ASO) moiety of the parent drug within 2 hours post-dose. On the other hand, no information was provided regarding the exposures of the THA linker and its major metabolite(s) in humans. In addition, the provided literature (Shemesh CS et. al.) on ADME of the THA linker is limited to animals. We recommend that you provide the PK information of the THA linker and its major metabolites in humans. Consider collecting PK samples longer than 2-hour post dose for measuring plasma concentrations of THA linker and its metabolites.

The need for further evaluations on the THA linker and its related metabolite(s) will depend on the characterization of the metabolism of ISIS 721744 and its THA linker through literature (your work and/or non-proprietary literature) and actual metabolism studies in monkey and mouse (as needed) to demonstrate reasonable comparability to human metabolism (see response to Question 1).

Discussion for FDA Response to Question 4:
The sponsor confirms that they will evaluate the THA linker metabolism in humans (b) (4) . Plasma samples up to 24 hours post-dose as well as urine and feces samples will be collected in humans to assess the abundance of THA-linker metabolites. The study result will be submitted later to the Agency.

Clinical

Question 5

Does the Agency agree with the overall design of the Phase 3 study, including:

- ***a) The target population, as defined by the key inclusion criteria?***
- ***b) The primary endpoint of HAE attack rate over 25 weeks vs. placebo?***
- ***c) The secondary endpoints?***
- ***d) The dosage and dose frequency, including a single dose level for adult and pediatric participants?***

FDA Response:

a) Overall, we agree with the target population and inclusion/exclusion criteria you propose. However, we recommend that you evaluate the efficacy and safety of ISIS 721744 in patients with mild-to-moderate hepatic impairment and/or pre-existing hepatic diseases for generalizability, particularly due to the following concerns:

I. A higher incidence of nonalcoholic fatty liver disease has been reported than is seen in the general population.

II. Patients with hepatic disease may have lower plasma PKK levels compared to healthy subjects due to impaired liver function and may have impaired uptake of drug. This indicates that ISIS 721744 may have differential effects in HAE patients with hepatic impairment.

III. Refer to FDA response to Question 3: the effect of hepatic impairment on the uptake, distribution, accumulation, and metabolism of ISIS 721744 is unknown. The potential for a different intra-hepatic cellular concentration of ISIS 721744 in patients with hepatic impairment may affect both efficacy and safety results in these patients.
We also recommend that you include patients with renal impairment, with an appropriate eGFR cutoff, in the proposed CS5 study, as also noted in the response to Question 3.

b) Your proposed primary endpoint is acceptable. Your final protocol should clearly specify the criteria used to define an HAE attack.

c) We have reviewed your proposed secondary endpoints and have the following comments.

I. We recommend ordering the secondary endpoints so that the most clinically meaningful endpoints are higher in the testing hierarchy (see FDA response to Question 8).

II. The secondary endpoints related to HAE attacks are proposed to be assessed from Week 5 to 25. Acknowledging your rationale that this delay allows time for the drug to take effect, we generally recommend that

clinical efficacy endpoints be evaluated starting from the first drug administration (Study Day 1 in your protocol).

III. *You propose the AECT and AE-QoL scores as secondary endpoints. While we acknowledge that HAE may have a negative impact on patients' health-related quality of life (HRQoL) and support the evaluation of disease control and quality of life measures in patients, we also note that HRQoL is a complex, multi-domain concept that can be challenging to measure, as it consists of concepts that might be influenced by factors beyond the treatment and consequently may not be sensitive to treatment effect. To date, we have not found the AE-QoL tool to be fit-for-purpose for the proposed context of use,* (b) (4) *To support your proposal of using each of these tools, submit the following information for Agency review and comment, prior to initiating your phase 3 trial:*

(1) *Conceptual framework of the instrument.*

(2) *Evidence of content validity (e.g., literature review, qualitative research with patients and expert clinicians) obtained for the specific context of use.*

(3) *Exact copy of the instrument as it will be administered during the clinical trial (e.g., electronic screen shots) and any associated training materials and user manuals.*

(4) *Proposed scoring algorithm(s) with rationale and corresponding information on how the instrument's scores will be analyzed as part of an endpoint.*

(5) *Plans for, and results from, evaluation of the psychometric properties and performance of the instrument (i.e., reliability, validity, and ability to detect change) after content validity has been established.*

(6) *Pre-specified plans for handling missing data.*

(7) *A priori threshold (or range of thresholds) representing clinically meaningful within patient improvement in the instrument's scores.*

IV. *The use of a total score for the AE-QoL instrument may be problematic as it consists of multiple domains (i.e., the functioning, fatigue/mood, fears/shame, and food domains) that includes items measuring distal*

concepts, making it difficult to interpret the score and describe clinical benefit.

V. *Because the AE-QoL was developed in adult patients, some of its items may not be applicable to adolescent patients (e.g., impairment of work). You will need to generate evidence of content validity of the AE-QoL in your target adolescent patient population by conducting concept elicitation and cognitive interviews to evaluate the content relevance, comprehensiveness, and clarity of the AE-QoL. You may also include your target adult patient population in the qualitative interviews to confirm the content validation of the AE-QoL. In addition, obtaining input from patients can help inform the endpoint selection and hierarchy.*

VI. *The threshold for meaningful within-patient change in the AE-QoL domain and total scores will need to be confirmed in the target adolescent and adult patient population. It is important to consider score interpretability of the improvement threshold(s) for both transformed scores and raw scores, i.e. whether the selected threshold(s) based on transformed scores also constitute a clinically meaningful within-patient change for the raw scores.*

d) *We agree that the proposed dosing regimen (Q4W) of ISIS 721744 aligns with the most commonly adopted dosing regimen for ASO drug products and is supported by your Phase 2 Study CS2. However, you did not adequately explore dose selection for ISIS 721744 in the target patient population prior to the proposed Phase 3 Study CS5; we note that only one dose level (80 mg) was investigated in Study CS2 in HAE patients. In addition, there is uncertainty in the extrapolation of dose-ranging PD results in healthy subjects from Study CS1 to HAE patients. We refer you to the dose-ranging comments conveyed in the Study May Proceed (SMP) Letter dated on Sep. 30, 2019, and we continue to strongly recommend that exploration of alternative, lower doses be performed as a key element of your development program.*

Additional Clinical Comments:

1. *You state that a home healthcare professional may perform assessments and procedures for the study. Clarify plans for training and oversight of the home healthcare staff.*

2. *Your protocol (p. 38) states that study drug may be delivered to participants at home. In general, we discourage this practice due to safety concerns, but there may be flexibility during the current public health emergency due to the COVID-19 pandemic.*

3. *We recommend that a physical examination be performed at each study visit, in particular to assess injection site reactions.*

Discussion for FDA Response to Question 5:
Ionis referred to their slide #25 which outlines the Agency comment to question 5(c) regarding AE-QoL and slides #27-29 which note that, although the instrument is not ideal, the phase 2 study showed significant results. (b) (4) Ionis intends to submit evidence to the IND file prior to phase 3 trials and will request Agency feedback. The FDA stated that the validation tool data needs to be submitted in order to evaluate the tool for its meaningfulness. Once the data is submitted, the DPACC will work with DCOA to provide feedback on the tool's reliability and interpretability. The FDA's review of the patient-reported outcome submission will likely take several months to complete. The FDA asked Ionis to clarify their timeline for submission and the start of phase 3 trials. Ionis stated they will provide a post-meeting email with an outline of timing.

Question 6
Does the Agency agree with the liver chemistry, renal function and platelet safety monitoring planned in the proposed Phase 3 study?

FDA Response:
Your monitoring plan for liver function, renal function, and platelet laboratory results generally appears adequate. We have the following specific comments:

1. *We note that the monitoring plan for platelets in your other IND programs for GalNAc-conjugated ASOs have incorporated a threshold of 100,000-125,000 platelets/mm3 to increase the platelet monitoring frequency to every 2 weeks. We recommend incorporating that action into your plans per protocol Table 2.*

Additional Comments Regarding Safety Monitoring*:*

1. *Because HAE patients are relatively healthy and the CTCAE grading scale is designed for assessing adverse events in cancer patients, for grading of adverse events relating to laboratory abnormalities, you should utilize an appropriate grading scale such as the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.*[1]

2. *As part of your safety monitoring plan, your protocol should include pre-specified rules to trigger a halt in enrollment to allow time for a review of safety data by the DSMB. The trial should be halted for a safety review based on these pre-specified criteria, such as:*

    a. *Death in any subject in which the cause of death is judged to be probably or definitely related to the study drug by the treating investigator;*

    b. *The occurrence in any subject of a life-threatening SAE that is assessed to be related to the study drug by the treating investigator;*

[1] https://www.fda.gov/media/73679/download

c. *Two occurrences of Grade 3 or higher toxicities that are assessed to be related to the study drug by the treating investigator;*

d. *Two occurrences of a clinically significant Grade 3 or higher laboratory abnormality assessed to be related to the study drug by the treating investigator.*

Discussion for FDA Response to Question 6:
There was no discussion held for FDA Response to Question 6.

Question 7
Does the Agency agree that the estimated size of the exposure database at the time of the NDA submission is adequate to support the proposed indication in this rare population?

FDA Response:
We acknowledge the rarity of HAE, but we also note the availability of several FDA-approved products for prophylaxis of HAE attacks. Your product is a new molecular entity with ligand-conjugation to direct the drug to hepatocytes; there is limited safety data available for this class of drugs. Therefore, we strongly recommend that you increase the size of your safety database; this could be achieved, at least in part, with the inclusion of additional doses in your trial. The adequacy of your safety database to provide substantial evidence of safety, relative to the benefit this drug provides to the patient population, would be a review issue.

Discussion for FDA Response to Question 7:
Ionis acknowledged the limited size of the safety database and stated an additional 20 subjects will be added to total 123 patients by the time the 120-day safety updated is due. Ionis referred to their slide #23 which outlined their justification of significant and adequate amount of safety exposure data. The FDA stated that we question the value of adding 20 additional patients from the open-label extension studies, as additional controlled safety data is needed. Extrapolation of safety results from other similar products and/or programs cannot be considered supportive and relevant for this program. The FDA recommends adding an additional dose cohort, or adding patients to the existing placebo-controlled study arms, to increase the sample size. Adding subjects from open-label extension studies is not acceptable. The Sponsor stated that if a new dose cohort is added for dose ranging, they might choose to pursue 2 different dose regimens (i.e., every 4 weeks versus every 8 weeks) rather than 2 different doses.

The FDA noted that the Ionis program has a much smaller safety database than other HAE programs, and that increasing the sample size to be comparable to other HAE programs should be feasible.

Biostatistics

Question 8
Does the Agency agree with the proposed statistical analysis in the pivotal HAE Phase 3 study for the primary and key secondary endpoints?

FDA Response:
We generally agree with your proposed statistical analysis, but have the following recommendations:

a) *We recommend conducting analyses using negative binomial regression model on the primary endpoint and some of the secondary endpoints, in addition to the Poisson regression model.*

b) *We recommend moving clinically meaningful endpoints, such as the number of patients with a clinical response defined as a ≥ 50%, ≥ 70%, or ≥ 90% reduction from Baseline (i.e., screening rate) in Investigator-confirmed HAE attack rate compared to placebo and the number of Investigator-confirmed HAE attacks requiring acute therapy compared to placebo, to higher in your proposed testing order.*
c) *Your proposed estimand appears reasonable, but you need to specify how to address your envisioned intercurrent events in the analysis. Submit Statistical Analysis Plan for review before your database lock.*

Discussion for FDA Response to Question 8:
There was no discussion held for FDA Response to Question 8.

Administrative/Regulatory

Question 9
Does the Agency agree that, if positive, a single pivotal study is acceptable for marketing approval in this rare disease?

FDA Response:
We acknowledge the rarity of the disease and the resultant challenges in obtaining evidence from multiple, large clinical trials. In general, evidence from at least two adequate and well-controlled studies is required to establish substantial evidence of effectiveness; however, in certain circumstances, a single adequate and well-controlled trial, particularly with confirmatory evidence, may be acceptable to support a licensing application. We refer you to the FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products[2] and the FDA Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products[3].

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-clinical-evidence-effectiveness-human-drug-and-biological-products
[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

ISIS 721744 is a new molecular entity; therefore, whether a single, well-controlled trial will be sufficient to provide substantial evidence of safety and effectiveness will depend on our review of your justification for reliance on a single trial, the submitted data, and the statistical and clinical persuasiveness of the treatment effect.

Additional Safety Comments:
We did not see a plan for your assessment of safety. To facilitate our review of the adequacy of the proposed development program for evaluating safety, provide the information listed below. You may consider including these elements in a program safety analysis plan (PSAP) for what will form your clinical summary of safety (see Crowe et al., 2009[4] for discussion on a PSAP) and in your protocol.

1. *Identification of potential key risks. The list of potential key risks should include those safety outcomes that are both: (1) plausibly affected by the drug, e.g., based on known/suspected effects of the drug class, biologically plausible off-target effects, non-clinical findings, or early-phase clinical findings; and (2) serious enough to potentially impact regulatory decision-making. Identifying such potential risks is important to ensure that they are reliably evaluated in your development program, acknowledging that the list of key risks may evolve over time, for example, if additional important signals are identified based on your phase 3 trial.*

2. *A plan for ascertaining (i.e., collecting data on) each key risk, including whether each outcome will be ascertained based on specific items in a structured checklist/questionnaire (active ascertainment) or based on a planned grouping of specific preferred terms (PTs) mapped from voluntary participant responses to open-ended questions (passive ascertainment).*

3. *Definitions of endpoints for the key risks, including any planned groupings of AEs, e.g., with Standardized MedDRA Queries (SMQs) or preferred terms (PTs) or System Organ Classes (SOCs) or some other grouping of multiple events/PTs representing the same or similar underlying concepts.*

4. *A high-level plan for analyzing safety including the following:*

    a. *A list of the safety outcomes that will be evaluated, including both key potential risks and other AEs/AE groupings that will be evaluated as part of the general safety evaluation.*

    b. *The summary measure(s) that will be used (e.g., cumulative incidence or incidence rate or some other measure).*

[4] Crowe *et al*. (2009) Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. *Clinical Trials*, 6: 430-440.

c. *Planned analyses to compare treatment groups with respect to the summary measure (e.g., with a risk difference, hazard ratio, or relative risk), along with an approach (e.g., a 95% confidence interval) to quantify the uncertainty in the treatment comparison. The goal of such analyses is to estimate treatment effects on safety outcomes, as well as uncertainty around those effects, not to perform hypothesis testing.*

5. *Any plans for integrated analyses of data from multiple studies, including the study groupings and methods for analysis. You should appropriately account for study differences and preserve the integrity of within-study randomization in integrated analyses to avoid confounding by study (e.g., Simpson's Paradox),[5] such as by adjusting for or stratifying by study.*

   Refer to the Discussion of the Safety Analysis Strategy for the ISS section below under Other Important Meeting Information.

Discussion for FDA Response to Question 9:
There was no discussion held for FDA Response to Question 9.

POST-MEETING COMMENTS:

1. Ionis provided the following information in an email dated August 30, 2021, and included this information in their September 8, 2021, meeting minutes submission to the Agency.

Submission Contents	Type of IND Submission	Estimated Timing of IND Submission
ISIS 721744-CS5 protocol amendment (incorporating changes due to the Type B meeting preliminary comments and meeting discussion)	Protocol Amendment: Change in Protocol	By end of September
Summary of the available THA linker metabolism data	Information amendment: clinical and pharmacology-toxicology	By end of September
Toxicologic assessment of liver findings from chronic repeat-dose toxicity study of ISIS 721744 in mice (Study 721744-AS04)	Information amendment: Pharmacology-toxicology	By mid-September

[5] Chuang-Stein, C. and Beltangady, M. (2011), Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies. *Pharmaceutical Statistics*, 10: 3–7.

Available evidence and validation plan for the AE-QoL	Information amendment: clinical	By end of October

2. We understand that you are planning to use ISIS 721744 injection as a prophylaxis to prevent attacks of hereditary angioedema (HAE) in patients 12 and older. However, you have not submitted a comprehensive risk analysis or your plans for a Human Factors (HF) validation study.

   We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

   Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

   Based on this risk analysis, you will need to determine whether you need to submit the results of a human factors (HF) validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product.

   If you determine that you do need to submit a HF validation study for your product, the risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

   Please refer to our draft guidance titled *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*[1] for the content of a human factors validation study protocol submission.

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in the following guidance documents[2]:

Applying Human Factors and Usability Engineering to Medical Devices

Guidance on Safety Considerations for Product Design to Minimize Medication Errors

Note that we published four draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling[3]:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

Bridging for Drug-Device and Biologic-Device Combination Products Guidance for Industry

3.0 OTHER IMPORTANT MEETING INFORMATION

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

[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.
[3] 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.

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 draft guidance for industry *Pediatric Study Plans: Content 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]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[8]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[9] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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[6] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[7] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

[8] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

[9] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[10]

[10] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion

needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[11] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[12]

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*.[13]

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling

[11] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[12] https://www.fda.gov/media/109533/download
[13] https://www.fda.gov/media/85061/download

changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified at the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Ionis Power Point presentation provided in the August 27, 2021, email. Ionis included the slide presentation in their September 8, 2021, meeting minutes.

39 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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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