Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases

Guidance for Sponsor-Investigators

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Ronald Wange at 301-796-1304.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmacology/Toxicology

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to describe the nonclinical information that FDA recommends to support an investigational new drug application (IND) for an antisense oligonucleotide being developed to treat a severely debilitating or life-threatening (SDLT) disease caused by a unique genetic variant where only a small number of individuals are prospectively identified (usually one or two). The investigational antisense oligonucleotide should be from a well-characterized chemical class[2] for which there is substantial nonclinical information and clinical experience that is publicly available or to which the sponsor-investigator (hereafter referred to as sponsor) has a right of reference.

This guidance is not intended to address nonclinical testing for commercial development of oligonucleotides.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] Examples of well-characterized antisense chemical classes, based on prior FDA experience, include single-stranded phosphorothioate or mixed phosphorothioate/phosphodiester with or without 2-methoxyethyl substituted oligonucleotides (by systemic or intrathecal route), and phosphorodiamidate morpholino oligonucleotides (by systemic route).

II. PROOF OF CONCEPT

Given that the administration of an investigational antisense oligonucleotide covered under this guidance will be to a small number of individuals with an SDLT disease, the nonclinical safety package recommended to support first-in-human (FIH) exposure is generally less extensive than what is typically recommended for development of antisense oligonucleotide products intended for broader use or use in less severe clinical circumstances.[3] To offset a greater assumption of risk due to more limited data, it is important that sponsors provide convincing in vitro and/or in vivo proof of concept (POC) data as part of any pre-investigational new drug (pIND) meeting package or the original investigational new drug (IND) submission (if no pre-IND meeting was requested) for investigational antisense oligonucleotides covered under this guidance. These data are important to support the potential for benefit for both adult and pediatric subjects.

III. IND-SUPPORTING SAFETY STUDIES

Sponsors should include the following nonclinical safety studies in their IND submission:

- Hybridization-dependent off-target assessment: Basic Local Alignment Search Tool (BLAST) and other appropriate in silico and/or in vitro assessments of possible off-target binding.

- Safety pharmacology: For systemically administered investigational antisense oligonucleotides, FDA recommends evaluating effects in the core safety pharmacology battery—cardiovascular, central nervous, and respiratory systems.[4] These endpoints may be assessed in the general toxicity study discussed below, if conducted in a rigorous manner (ICH S7A). If a pharmacologically relevant species is available, sponsors should use that species.

  – In vitro human ether-a-go-go-related gene (hERG) testing is generally not warranted.

  – For products delivered directly to the central nervous system (e.g., intrathecally), the safety pharmacology assessment may be limited to central nervous system endpoints.

[3] FDA regulations provide flexibility in applying regulatory standards because of the many types and intended uses of drugs. FDA "exercise[s] its scientific judgment" in determining the kind and quantity of data a sponsor is required to provide for individual drug development programs. See, for example, 21 CFR 314.105(c). This flexibility extends from the early stages of development to the design of adequate and well-controlled studies required to demonstrate effectiveness to support marketing approval and to establish safety data needed for the intended use. For further information on this topic, see the draft guidance for industry *Rare Diseases: Common Issues in Drug Development* (January 2019). 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/regulatory-information/search-fda-guidance-documents.

[4] See the ICH guidance for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals* (July 2001). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

FDA recommends that these endpoints be assessed following initiation of dosing and again toward the end of the study.

  - If the route of administration does not result in significant systemic or central nervous system exposures (e.g., intravitreal administration), safety pharmacology studies are generally not warranted.

- Genotoxicity: Genotoxicity assessment is generally not warranted.

- General toxicity

  - In combination with the results from the POC and safety pharmacology assessments, a single, adequately designed, good laboratory practice–compliant general toxicity study can support FIH dosing. The toxicity study can be conducted in a rodent or nonrodent species.[5] Sponsors should provide scientific justification for the species selected. If a pharmacologically relevant species is available, sponsors should use that species.

  - The study should assess a standard battery of toxicological endpoints, including clinical observations, body weight, food consumption, clinical pathology, toxicokinetic analysis, and histopathology of a comprehensive panel of tissues.

  - The route of administration used in animal studies should be the same as the intended clinical route. Sponsors should provide justification if an alternative route is proposed for the toxicity study.

  - To the extent feasible, the drug formulation used in animal studies should be comparable to the clinical formulation.

  - The dosing regimen (i.e., dose levels and frequency of dosing) should provide adequate coverage for the expected clinical exposure with regard to both starting dose and maximum anticipated dose. To allow for the greatest flexibility in clinical dose selection, it is preferable for the high dose to be a maximally tolerated or maximum feasible dose. Sponsors should justify selecting an alternative basis for high-dose selection.[6]

  - To ensure that the toxicity study can meet its objectives, FDA recommends that sponsors submit a draft protocol of the toxicity study to FDA for review and feedback before initiating a study.

[5] We support the principles of the 3Rs, to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method is adequate to meet the regulatory need.

[6] See the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010).

A. Duration and Timing of General Toxicity Studies

In the context of an investigational antisense oligonucleotide covered by this guidance, a single 3-month toxicity study is considered adequate to assess safety for initiating human dosing, dose-escalation, and chronic treatment.

For the clinical phenotype of rapid progression to death or rapid progression to substantial irreversible morbidity (e.g., within 1 year):

- The IND submission should include at least 2 weeks of in-life data generated from an ongoing 3-month toxicity study.
  - Interim data should be provided periodically (e.g., monthly). Sponsors must expeditiously report to the FDA findings suggesting a significant risk to the study participant(s) (21 CFR 312.32(c)(1)(iii)). The institutional review board should likewise also be promptly informed of any such finding(s).[7]
- A complete draft 3-month study report should be submitted as soon as completed. Sponsors should submit the final study report within 120 days of submitting the draft report.
  - Submission of the full study report should support continued dosing and dose escalation, assuming the data continue to support a conclusion of reasonable safety.

B. For the Clinical Phenotype of Slower Progression

- A completed 3-month toxicity study report should be submitted with the initial IND.

IV. FIH DOSE SELECTION

The primary goal of selecting the starting dose is to identify a dose that is expected to have pharmacologic effects and is reasonably safe, and it should be scientifically justified based on the totality of available data.

Sponsors should clearly describe and justify the method used for selecting the starting dose, including the basis for calculating safety margins between doses tested in animals and the dose or doses selected for administration in a human. For local administration, sponsors should take into consideration organ weight, volume, or other measures as appropriate for interspecies dose scaling. And for intrathecal administration, sponsors should calculate interspecies dose comparisons based on a dose normalized to cerebrospinal fluid volume.

[7] For additional guidance on safety reporting, see the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012).

V. DOSE ESCALATION

When a steep dose-response or an exposure-response for severe toxicity is observed in nonclinical toxicity studies, or when no preceding marker of severe toxicity is available, sponsors should consider smaller than usual dose increments (e.g., fractional increments rather than dose doubling) for clinical dosing.

For investigational antisense oligonucleotides within the scope of this guidance, the highest dose or exposure assessed in the nonclinical studies does not necessarily limit the highest dose that can be evaluated in humans, depending on the available nonclinical and clinical information and the participant's clinical situation.

VI. FACTORS SUPPORTING ABBREVIATED NONCLINICAL ASSESSMENT APPROACH DESCRIBED IN THIS GUIDANCE

The nonclinical safety package described here differs from that generally recommended for non-SDLT diseases, for treatment modalities other than antisense oligonucleotides, and for SDLT diseases with larger patient populations. FDA considers the nonclinical safety package recommended in this guidance acceptable to support INDs for investigational antisense oligonucleotides within the scope of this guidance, in part because of existing experience with antisense oligonucleotides and the ability to anticipate and manage some of the potential adverse effects. However, the probability of identifying toxicity nonclinically may be reduced in comparison to standard nonclinical safety testing, and the potential for clinically significant adverse effects may therefore be increased. With appropriate disclosures in the informed consent, this increased risk is considered acceptable to FDA at this time in the context of an investigational antisense oligonucleotide covered by this guidance.

Expansion of this approach to other oligonucleotide chemistries or mechanisms of action (e.g., siRNA), or to other treatment modalities (e.g., individualized biologics) should be supported by a nonclinical approach that provides a similar understanding of the chemistry and mechanism of action sufficient to allow for safe FIH dose selection, potential dose escalation, and an ability to predict the likely adverse effects that could occur, and how these can be clinically monitored. This will be considered by FDA on a case-by-case basis.

Expansion to a larger population or an intent to commercialize a treatment would typically warrant additional studies (e.g., longer duration general toxicity studies).[8]

[8] See ICH guidances for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012), *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010), and ICH M3(R2).