Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology Guidance and Policy at CDER_OCP_GPT@fda.hhs.gov.

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

June 2022
Clinical Pharmacology

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

This guidance provides recommendations to assist industry in the development of oligonucleotide therapeutics under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR parts 312 and 314. Specifically, this guidance represents the FDA's recommendations for certain evaluations including pharmacokinetic, pharmacodynamic, and safety assessments during oligonucleotide therapeutic development, including: (1) characterizing the potential for QTc interval prolongation, (2) performing immunogenicity risk assessment, (3) characterizing the impact of hepatic and renal impairment, and (4) assessing the potential for drug-drug interactions. This guidance provides recommendations on when to conduct these assessments and what types of assessments are suitable to address these questions.

Oligonucleotide therapeutics are an emerging therapeutic modality with increasing numbers of drugs in development.[2] Antisense and small interfering RNA (siRNA) oligonucleotide therapeutics have been FDA-approved in recent years to treat rare diseases; in addition, many oligonucleotide therapeutics are currently in development to treat common chronic diseases.

Oligonucleotide therapeutics include a wide variety of synthetically modified RNA or RNA/DNA hybrids that are specifically designed to bind to a target RNA sequence to alter RNA and/or protein expression. Even within the therapeutic modality, oligonucleotide therapeutics can differ in several ways, including but not limited to:

- Mechanism of action (e.g., splice modulating, RNA interference, RNase H-mediated cleavage)

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

[2] Rogers H, O Adeniyi, A Ramamoorthy, S Bailey, and M Pacanowski, 2021, Clinical Pharmacology Studies Supporting Oligonucleotide Therapy Development: An Assessment of Therapies Approved and in Development Between 2012-2018, Clin Transl Sci,14(2):468-475.

- Structure (e.g., single-stranded RNAs, double-stranded RNAs or RNA/DNA hybrids)

- Chemical modifications to the base and/or backbone

- Size

- Sequence

- Delivery strategy (e.g., lipid nanoparticles, liposomes, other polymeric nanoparticles, polyethylene glycol (PEG), N-acetylgalactosamine (GalNAc))

- Presence or absence of other moieties (e.g., small molecule, proteins, antibodies)

The recommendations in this guidance generally apply to oligonucleotide therapeutics that use an RNA-centric mechanism of action. Providing recommendations based on any specific characteristics (e.g., backbone modification, specific conjugation) is beyond the scope of this guidance. This guidance is based on the knowledge gained in the development of oligonucleotide therapeutics submitted to the Agency in new drug applications (NDA) as of the date of this guidance. As the development of oligonucleotide therapeutics evolve (e.g., chemical modifications to the base and/or backbone, structure, delivery strategy), sponsors should contact appropriate review Divisions for questions related to the topics in Sections II.A through D of this guidance.

Oligonucleotide therapeutics that use mechanisms of action such as direct modulation of proteins (e.g., aptamers) or immunostimulation (e.g., TLR9 agonists) are beyond the scope of this guidance. The FDA encourages sponsors to communicate with appropriate review Divisions during the pre-investigational new drug application (pre-IND) or investigational new drug application (IND) stage to discuss the development of these therapeutics.

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.

II. CLINICAL PHARMACOLOGY CONSIDERATIONS

Oligonucleotide therapeutics generally are cleared rapidly from systemic circulation. However, these drugs have longer tissue and pharmacodynamic half-lives. Therefore, several factors should be considered in determining which studies are needed to characterize the clinical pharmacology of these products.

In general, sponsors should characterize the plasma pharmacokinetics of an oligonucleotide therapeutic following single and multiple doses early in drug development. However, for some

oligonucleotide therapeutics, plasma pharmacokinetics might not reflect the target tissue distribution, pharmacodynamics, safety, or efficacy. Therefore, in multiple-dose studies, sponsors should include an assessment of appropriate pharmacodynamic biomarkers (e.g., target mRNA, target protein, or a downstream biomarker that reflects modulation of the target protein) or consider other response measures. Such assessments are important in situations where pharmacodynamic changes are independent of plasma pharmacokinetic changes. The selection of the pharmacodynamic endpoints should be discussed with the appropriate FDA review staff, especially in cases where the pharmacodynamic endpoints might not directly reflect target knockdown (e.g., cerebrospinal fluid for central nervous system targets).

Oligonucleotide therapeutics have certain unique characteristics compared to small molecule or biological products (e.g., chemistry, structure, sites of action, pharmacokinetic disposition, pharmacodynamics). Therefore, sponsors should consult Sections II.A. to II.D. below for considerations when characterizing QTc interval prolongation, performing immunogenicity risk assessment, assessing the impact of hepatic and renal impairment, and determining the potential for drug-drug interactions during oligonucleotide therapeutic development.

Specific considerations should be given to the chemistry (e.g., backbone modification, conjugation), drug target, plasma protein binding, and route of administration as these factors determine the distribution of the oligonucleotide therapeutic to the liver, kidneys, and other tissues as well as determine the exposure (local or systemic) to the drug.

Additionally, appropriate bioanalytical methods should be used to characterize the parent oligonucleotide and any relevant metabolites, including chain-shortened metabolites. Refer to the FDA guidance entitled *Bioanalytical Method Validation* (May 2018) for additional details.[3]

A. Characterizing QTc Interval Prolongation and Proarrhythmic Potential

To date, no large mean effect of oligonucleotide therapeutics on the QTc interval has been observed in the small number of dedicated QT studies reviewed by the FDA. However, given that oligonucleotide therapeutics are a diverse group of drugs (see Section I), available clinical experience does not adequately support providing an overall conclusion on the proarrhythmic potential of specific types of oligonucleotide therapeutics (e.g., based on chemistry or delivery strategies).

An assessment of QT prolongation risk and a proposed QT assessment plan should be submitted for all oligonucleotide therapeutic development programs as outlined in the FDA guidance entitled *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2012) and the *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers (R3)* (June 2017). All proposals in the QT assessment plan should be adequately justified and discussed with the Agency. The timing and extent of the clinical QT assessment depend upon the overall benefit/risk profile of the oligonucleotide therapeutic.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page https://www.fda.gov/regulatory-information/search-fda-guidance-documents

B. Performing Immunogenicity Risk Assessments

An unwanted immune response to an oligonucleotide therapeutic can be generated to the carrier, backbone, oligonucleotide sequence, or any novel epitopes created from the whole drug (carrier plus oligonucleotide). The development of oligonucleotide therapeutics is rapidly evolving, and new chemistries, modifications etc. can significantly affect the immunogenicity risk and clinical immunogenicity assessment of a particular product.

The clinical immunogenicity assessment for an oligonucleotide therapeutic should follow a risk-based approach and be included in a product-specific immunogenicity risk assessment as outlined in the FDA guidance entitled *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014). Some considerations when determining the immunogenicity risk of an oligonucleotide therapeutic include, but are not limited to:

- **Product factors**: base sequence, base modification, backbone modification, strandedness, purity, modified nucleotides, secondary and tertiary structures, and carrier components (e.g., PEGylated lipid nanoparticles)

- **Pharmacology of the product**: mechanism of action, cell/tissue target, expression profile, route of administration, dosing regimen (chronic versus acute)

- **Patient characteristics**: immune activation status of the population (e.g., auto-immune or inflammatory conditions), concomitant medications (ability to influence the incidence or clinical impact of anti-drug antibodies (ADAs) (e.g., immunosuppressants such as chemotherapy)

The clinical assessment of immunogenicity for oligonucleotide therapeutics usually includes a multi-tiered immunogenicity assay assessment as outlined in FDA guidance.[4] As determined by the immunogenicity risk assessment, it may be appropriate to develop multiple immunogenicity assays to measure immune responses to the different components of an oligonucleotide therapeutic, such as the carrier component (e.g., PEGylated lipid nanoparticles) and/or oligonucleotides conjugated to protein targeting ligands (e.g., Fab fragments). In addition, the mechanism of action of some oligonucleotide therapeutics generates a modified protein (e.g., splice-altering, exon-skipping oligonucleotide therapeutics); in such cases, the sponsor should consider an immunogenicity assay measuring antibodies to the modified protein.

Additionally, unwanted innate immune activation should also be measured when appropriate (e.g., oligonucleotide therapeutic-induced cytokine release, presence of sequences that are known to be immunogenic in humans such as GU, CpG or 5'-P, presence of natural nucleosides with 2'-deoxy, 2'-OH or unmethylated C).

For clinical immunogenicity assessments, immunogenicity sample collection should coincide with pharmacokinetic and pharmacodynamic sampling time points to evaluate whether ADAs

[4] See the FDA guidance *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection* (February 2019).

impact the pharmacokinetics, pharmacodynamics, and any immune-mediated adverse events of the oligonucleotide therapeutic. It is also important to evaluate samples to determine if the oligonucleotide therapeutic interferes with ADA testing. Of note, as determined by the immunogenicity risk assessment, it may be adequate to bank samples in early development (e.g., Phase 1/ First-in-human studies) for later testing if there is new evidence of altered pharmacokinetics, pharmacodynamics, or immune-mediated adverse events. Sponsors should discuss their immunogenicity risk assessment and how it informs their clinical immunogenicity assessment for a particular product with the Agency.

In certain circumstances, the FDA could also recommend assessing for nucleotide sequence-specific antibodies and/or bioactivity (e.g., neutralization, enhancement). Any recommendations for these assays will be informed by clinical concerns, such as oligonucleotide sequence cross-reactivity, novel structures, or modifications and should be discussed with the relevant review Division on a case-by-case basis.

C. Characterizing the Impact of Organ Impairment on Pharmacokinetics, Pharmacodynamics, and Safety

To determine the appropriate approach for characterizing the impact of organ function on the pharmacokinetics, pharmacodynamics, and safety of the oligonucleotide therapeutic, the sponsor should identify the role of the liver and kidney in the disposition and elimination of the oligonucleotide therapeutic by considering in vitro, preclinical, and early Phase 1 clinical data. These early assessments, along with safety and tolerability information, should be used to inform the enrollment of subjects with a full range of hepatic and/or renal function in the late-phase trials. In addition, in subjects with organ impairment, it is important to consider the impact of changes in expression and turnover of: (1) the target of the drug; and (2) in the case of conjugated oligonucleotide therapeutics, the target of the conjugate that determines the disposition of the drug to the liver or kidneys (e.g., receptors expressed in liver or kidney that allow for targeting of the drug to those organs).

When the oligonucleotide therapeutic is not predominantly renally cleared or does not target the liver, the sponsor should enroll subjects with a full range of renal or hepatic function, respectively, in late-phase trials based on information from nonclinical studies and early clinical experience. The sponsor should provide appropriate justification if subjects with impaired renal or hepatic function are excluded from late-phase trials.[5]

When the oligonucleotide therapeutic is substantially renally cleared (i.e., 30 percent or more of the systemically available drug is excreted unchanged in urine), further characterization of the impact of renal impairment is recommended.[6] In such situations, different strategies can be used to study the impact of renal impairment on response and drug exposures. A reduced

[5] See the FDA guidance entitled *Enhancing the Diversity of Clinical Trial Populations —Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

[6] See the FDA draft guidance entitled *Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling* (September 2020). When final, this guidance will represent the Agency's current thinking on this topic.

pharmacokinetic study design can be considered to assess the impact of severe renal impairment on the pharmacokinetics, pharmacodynamics, tolerability, and safety of the oligonucleotide therapeutic. When applicable, this study should be a multiple-dose study to enable adequate characterization of pharmacodynamic effects. The findings from such a study can inform any additional characterizations as well as the inclusion/exclusion criteria for subsequent late-phase trials. With appropriate justification, other alternative approaches can also be considered.[7]

When the oligonucleotide therapeutic targets the liver, the sponsor can consider alternative approaches that allow for sequential or adaptive enrollment starting in early phase studies of tolerability, safety, and pharmacodynamics.[8] The sponsor should consider the degree of portal hypertension and shunting of blood flow around the liver in these studies. This information can be used to facilitate the enrollment of subjects with a range of hepatic function in late-phase clinical trials.

Because changes in organ function can result in pharmacodynamic changes that are independent of pharmacokinetic changes, whenever appropriate and feasible, the sponsor should conduct pharmacodynamic assessments. When appropriate, population pharmacokinetic-pharmacodynamic modeling can help assess the correlation between organ impairment and pharmacodynamics, other biomarkers, safety, or efficacy data. Unless there is adequate justification (e.g., safety concerns), a sufficient number of subjects over a range of organ function should be enrolled across the drug development program to obtain meaningful data in all categories of organ function.

D. Considerations for Assessing Drug Interactions

1. Pharmacokinetic Interactions with Cytochrome P450 Enzymes and Transporters

a. Oligonucleotide therapeutics as substrates for cytochrome P450 enzymes and transporters

Oligonucleotide therapeutics are not typically metabolized by cytochrome P450 (CYP) enzymes. These drugs are primarily metabolized by endonucleases and exonucleases or are chemically modified to resist degradation. Therefore, the disposition of oligonucleotide therapeutics is not anticipated to be affected by inhibitors or inducers of CYP enzymes. Additionally, modulation of efflux transporters such as P-gp and BCRP, hepatic uptake transporters such as OATP1B1 and OATP1B3, or renal uptake or efflux transporters such as OAT1, OAT3, OCT2, MATE1, and MATE2/K are generally not anticipated to have a significant impact on the pharmacokinetics of

[7] Refer to the FDA draft guidance entitled *Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling* (September 2020) for additional information on alternative approaches. When final, this guidance will represent the Agency's current thinking on this topic.

[8] For more information on sequential analysis, refer to the concepts mentioned in the following article: Sahre MD, L Milligan, R Madabushi, RA Graham, KS Reynolds, A Terzic, J Benjamin, GJ Burckart, SM Huang, R Schuck, AM Thompson, and I Zineh, 2021, Evaluating Patients With Impaired Renal Function During Drug Development: Highlights From the 2019 US FDA Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting, Clin Pharmacol Ther, 110(2):285-288.

oligonucleotide therapeutics. If the oligonucleotide therapeutic undergoes substantial renal active secretion as an unchanged drug, it could be important to evaluate whether an oligonucleotide is a substrate of renal transporters in vitro.[9]

b. Oligonucleotide therapeutics as modulators of CYP enzymes and transporters

Evaluating the drug interaction liability of oligonucleotide therapeutics as inhibitors and inducers of CYP enzymes or drug transporters usually begins with in vitro assessments. Refer to the FDA guidance entitled *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) for general considerations when conducting in vitro experiments and interpreting data. Because differences among the various in vitro systems have been reported, sponsors should carefully select the appropriate in vitro systems to evaluate drug interactions.[10] Based on current experience, oligonucleotide therapeutics either do not modulate or minimally modulate the major CYP enzymes and drug transporters. However, an overall recommendation for specific types of oligonucleotide therapeutics (e.g., based on chemistry or delivery strategies) cannot be provided at this time. The sponsor should provide adequate justification if in vitro assessments of oligonucleotide therapeutics as perpetrators in drug-drug interactions are not conducted.

There are other possible mechanisms for interactions between oligonucleotide therapeutics and CYP enzyme or transporters. The potential of an oligonucleotide therapeutic to modulate CYP enzymes or transporters directly (e.g., via off-target hybridization with CYP enzyme or transporter mRNA transcripts) or indirectly (e.g., by interfering with the synthesis or degradation of heme or by modulating cytokines) should be evaluated.

If studies indicate that the oligonucleotide therapeutic could modulate CYP enzymes or transporters, the sponsor should consider clinical studies to evaluate in vivo drug interactions. For general considerations on study design and conduct, refer to the FDA guidance entitled *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry* (January 2020).

2. Pharmacodynamic Interactions

Oligonucleotide therapeutics can exhibit pharmacodynamic interactions with a concomitant drug when the pharmacological effect of one drug is altered by that of another drug (e.g., drugs with shared mechanism of action pathways). Because such interactions may be unique to individual therapeutics, the sponsor is encouraged to consult with the relevant review Division regarding assessment of pharmacodynamic drug interactions.

[9] See the FDA guidance entitled *In Vitro Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

[10] Kazmi F, P Yerino, C McCoy, A Parkinson, DB Buckley, and BW Ogilvie, 2018, An Assessment of the In Vitro Inhibition of Cytochrome P450 Enzymes, UDP-Glucuronosyltransferases, and Transporters by Phosphodiester- or Phosphorothioate-Linked Oligonucleotides, Drug Metab Dispos, 46:1066-74.