Advanced Prostate Cancer: Developing Gonadotropin-Releasing Hormone Analogues

Guidance for Industry

DRAFT GUIDANCE

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

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 describes the Food and Drug Administration's (FDA's) current recommendations regarding the overall development program to establish the effectiveness and safety of gonadotropin-releasing hormone (GnRH) analogues for treating advanced prostate cancer.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

GnRH analogues, both agonists and antagonists, remain a mainstay for treating patients with prostate cancer. Both are intended to reduce testosterone (T) levels in the blood, a major driver of prostate cancer growth, but they have different properties. GnRH agonists cause a transient surge in luteinizing hormone (LH) and testosterone. This surge desensitizes the LH receptors and is followed by a sustained decrease in T levels. Patients whose LH receptors have not been fully desensitized will develop a surge in testosterone during subsequent administration of a GnRH agonist. This increase is referred to as the acute-on-chronic effect. GnRH antagonists bind to the

[1] This guidance has been prepared by the Division of Oncology Products 1 in the Center for Drug Evaluation and Research at the Food and Drug Administration.

GnRH receptor, preventing production of LH and the resultant production of testosterone. Subsequent administration of a GnRH antagonist does not result in a testosterone surge.[2]

New drug applications for GnRH analogues typically rely, in part, on FDA's finding of safety and/or effectiveness for a previously approved GnRH analogue and are submitted through the pathway described by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. These 505(b)(2) applications generally have included product-specific data from a clinical trial and nonclinical general toxicology studies. This guidance addresses the current regulatory requirements for the approval of these agents and the use of a standardized approach to trial design.

III. DEVELOPMENT PROGRAM

A. Product Development

GnRH analogues typically contain a peptide similar to naturally occurring GnRH. The product is often marketed in the form of a polymer (such as freeze-dried powder (microspheres) that a provider must mix with a solvent in a prefilled syringe to be reconstituted into a suspension) in a single-dose delivery system for intramuscular administration. Chemistry, manufacturing, and controls (CMC) information for this peptide and the materials necessary to provide an extended-release formulation can be provided within an application or as a cross reference to a drug master file. The CMC information submitted in the investigational new drug application (IND) during drug development should follow relevant FDA guidance documents:

- Guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products*[3] (November 1995)

- Guidance for industry *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information* (May 2003)

For products entering clinical trials, the product development program should be aligned with the following applicable ICH guidance documents:

- Guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003)

- Guidance for industry *Q1B Photostability Testing of New Drug Substances and Products* (November 1996)

[2] TN Clinton, SL Woldu, and GV Raj, 2017, Degarelix versus Luteinizing Hormone-Releasing Hormone Agonists for the Treatment of Prostate Cancer, Expert Opin Pharmacother 18(8): 825–832; LG Gormella, 2009, Effective Testosterone Suppression for Prostate Cancer: Is There a Best Castration Therapy?, Rev Urol 11(2): 52–60.

[3] 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.

- Guidance for industry *Q2(R1) Validation of Analytical Procedures: Text and Methodology* (November 2005)

- Guidance for industry *Q3A(R) Impurities in New Drug Substances* (June 2008)

- Guidance for industry *Q3B(R2): Impurities in New Drug Products* (July 2006)

- Guidance for industry *Q3C Impurities: Residual Solvents* (December 1997)

- Guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000)

Because the active ingredient is intended to be released over 1 to 6 months, ensuring adequate and continuous product release is critical to successful development. During product development, in vitro tests are conducted to evaluate and characterize the quality and performance of the proposed drug products. The in vitro drug-release characteristics should correlate with the in vivo drug-release performance, and clinically relevant drug-release acceptance criteria should be selected to ensure consistent quality, efficacy, and safety. In vitro drug-release testing can also be used to evaluate changes in formulation (e.g., polymer and excipient selection) and the manufacturing process (e.g., equipment parameter changes) during product development and potential scale-ups. The in vitro drug-release tests are often used to monitor the quality of the product at release and over time, and they are intended to provide evidence that the product will perform consistently throughout its shelf life. For products for which drug release is expected to occur over a long duration, developing an accelerated in vitro drug-release method is an option for drug product release and stability testing. Sponsors should characterize in vitro drug release early in product development and should make it available at initial IND submission for FDA feedback. See the appendix for additional information.

When a delivery or mixing device is used, sponsors should describe the drug-delivery device and reference an approved or cleared device or device application. Sponsors should also ensure that the performance characteristics of the syringe are maintained throughout the shelf life. In-use testing should be considered.

B. Nonclinical Development

Nonclinical development of anticancer pharmaceuticals is described in the following guidance documents:

- ICH guidance for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers* (June 2018)

- ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (June 2011)

- Guidance for industry *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations* (May 2019)

Sponsors should include pharmacology studies supporting the proposed trial with the initial IND. It is important to test the formulation in an animal model for dose finding and chemistry and manufacturing consistency before initiating clinical trials. In general, sponsors should provide nonclinical general toxicology studies in rodents and nonrodents of up to 1 month's duration to support phase 1 and phase 2 development, and they should provide studies of 3 months' duration to support phase 3 or pivotal registration trials. Safety pharmacology and toxicokinetic endpoints may be included in these studies rather than using stand-alone studies. The general toxicology studies should use a route of administration similar to the route of administration in the intended clinical trial and should follow the recommendations described in Table 1 of ICH S9. Consistent with ICH S6(R1), if the 1-month studies show a consistent toxicological profile, then a 3-month study in a single species may be sufficient. Because GnRH analogues are peptides with expected high specificity, secondary pharmacology studies are usually not warranted.

Consistent with the FDA guidance on reproductive testing for oncology pharmaceuticals, no embryo-fetal toxicology study or other reproductive toxicology study is needed to support the indication of advanced prostate cancer (see ICH S9, ICH S6(R1), and *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations*). Unless there are nonconventional amino acids in the GnRH product, there is no need to evaluate genotoxicity or carcinogenicity.

In general, it is not necessary to evaluate phototoxicity or immunotoxicity to support developing or marketing GnRH analogues to treat advanced prostate cancer.

C. Phase 3 Efficacy Trial Considerations

1. Trial Design

Sponsors should conduct single-arm trials using T levels as surrogate endpoints to support the approval of GnRH analogues. These trials should demonstrate the following:

- Attainment of a castrate (<50 ng/dL) T level
- Maintenance of castrate T levels until the end of a dosing interval
- Maintenance of castrate T levels immediately after later doses (not the first dose) of the study drug

To demonstrate these effects of the study drug on T levels, the treatment period should be at least twice as long as the dosing interval. For products that act over a relatively short period (e.g., 1 month), the treatment period should extend over several (three to four) dosing intervals.

Sponsors should discuss with the division randomized designs intended to support comparative claims (efficacy and/or safety) among GnRH analogues or long-term safety of an individual

agent. Sponsors should also discuss with the division trials for indications other than treating advanced prostate cancer before initiation.

2. Trial Population

Patients enrolled in studies intended to support an indication for treating advanced prostate cancer should have normal age-adjusted T levels and metastatic disease. Limiting the population to the metastatic disease setting provides a more accurate assessment of the safety profile in the intended population. For example, the incidence of tumor/bone flare cannot be assessed in patients who do not have metastatic bone disease. Although the safety profile of GnRH analogues is thought to be well-known, the incidence of events such as bone flare have been incompletely explored and differences between medications have been poorly characterized. Assessing adverse events in a population with metastatic prostate cancer allows accurate information to be communicated to patients and practitioners concerning the adverse event profile in the intended population. We recommend that information concerning the patient's history of prostate cancer be recorded, including the date of diagnosis, current stage, extent of metastatic disease at baseline, and prior therapies.

3. Dose Selection

The study drug dose used in the clinical trial should be informed by nonclinical testing. Sponsors should consider using early dose-finding studies or enrolling patients at multiple dose levels in the phase 3 trial. Usually, one phase 3 trial is sufficient to support approval of a 505(b)(2) application that relies, in part, on FDA's finding of safety and/or effectiveness for a listed drug because there is extensive clinical experience concerning GnRH analogues.

4. Trial Procedures and Timing of Assessments

GnRH agonists are expected to achieve castrate T levels by Day 28, so T levels should be measured at this time. GnRH antagonists are expected to achieve more rapid development of castrate T levels than GnRH agonists. To document this, sponsors should consider weekly assessment of T levels until Day 28. Although the final analyses should use T levels assessed at a central laboratory, T levels should also be assessed at local laboratories so that patients who do not have castrate T levels (on or after Day 28) can be promptly removed from the trial for safety reasons.

To ensure that castrate T levels are maintained over the dosing interval, sponsors developing GnRH agonists or antagonists should measure T levels before each dose of study drug. Sponsors could consider additional measurement of T levels at other time points, including the midpoint of the dosing interval, to help guide further drug development if the pre-dose level fails to show castrate T levels.

To assess the acute-on-chronic effect of additional doses of a GnRH agonist on the T level, sponsors should obtain T levels 1 hour, 4 hours, and 3 days after later doses (i.e., not the first dose) in all patients. Sponsors could consider an additional measurement 7 days after the additional dose. Three-day or 7-day levels will provide information concerning the duration of

the acute-on-chronic effect in all patients. T, rather than LH or follicle-stimulating hormone, levels should be used to assess the acute-on-chronic effect. Sponsors should justify and discuss the appropriateness of the timing of T-level assessments with the Agency before initiating the study.

We recommend that sponsors assess the effect of the study drug on tumors by measuring prostate specific antigen (PSA) and reviewing bone scans and scans of known sites of disease (e.g., CT scans). Tumor measurements would normally be obtained in these patients every 3 to 6 months during the treatment period, and we recommend that these be included in the database for an application.

Sponsors should collect information on the dates of use and dose of herbal medications and dietary supplements, if they were used, at study entry and throughout the treatment period because some herbal or alternative medications may affect T levels. Sponsors should also provide patients with a list of medications that they should not use during the study period.

Adverse event collection should include the use of open-ended questions and the collection of solicited adverse events such as hot flush, breast pain, bone pain, difficulty sleeping, and injection site reactions. After collecting data on injection site reactions, sponsors should report all terms related to this concept (e.g., injection site swelling, redness, pain, etc.) under a single term. The incidence of injection site reactions has varied markedly between trials, and this may be related to a lack of uniformity in ascertainment and assessment. Sponsors should assess adverse events throughout the treatment period and for 30 days after the end of the dosing interval. For example, sponsors should assess adverse events for 4 months after the last dose of a 3-month formulation of a GnRH analogue.

Sponsors should discuss the potential use of patient-reported outcomes to support labeling claims with the division before initiation.

5. Pharmacokinetics and Pharmacodynamics

Plasma T levels have typically been used as surrogate endpoints leading to traditional approval of GnRH analogues for advanced prostate cancer.[4] A robust bioanalytical method for measuring plasma T levels is therefore critically important. Sponsors should employ a fully validated bioanalytical assay for the analysis of plasma T levels. Sponsors are responsible for ensuring that bioanalytical methods measuring the plasma T levels are accurate, precise, specific, sensitive, and reproducible. A separate FDA guidance for industry is available to guide bioanalytical method validation (*Bioanalytical Method Validation* (May 2018)).

Given the use of a pharmacodynamic surrogate endpoint (T level) in the clinical trial to support approval, sponsors need not demonstrate pharmacokinetic (PK) bioequivalence of the study drug to the listed drug on which the sponsor intends to rely in a proposed 505(b)(2) application.

[4] The term *traditional approval* denotes the long-standing route of drug approval based on the demonstration of clinical benefit or an effect on a surrogate endpoint known to predict clinical benefit. That term is distinguished from accelerated approval, which is associated with use of a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit to support drug approval.

However, we recommend that PK samples of the study drug and the listed drug be collected in a pilot study or a subgroup of the registration trial. Adequately characterized PK profiles of the study drug helps the Agency understand the drug release and accumulation potential after multiple doses.

6. Efficacy Endpoints

Plasma T level is used as a validated surrogate endpoint to assess the efficacy of GnRH analogues. A T level < 50 ng/dL is considered castrate level. The timing of T level assessments is discussed above. To accommodate T level assessments at the end of a dosing interval, sponsors should extend the study period for at least two dosing intervals for long-acting (3 to 6 months) formulations and three to four dosing intervals for short-acting (1 month) formulations.

Assessing mean T levels would not provide an adequate measure of drug efficacy because averaging T levels will not reveal the patients who did not benefit (i.e., achieve castrate levels); therefore, it is critical to show that a high percentage of patients achieved and maintained a T level < 50 ng/dL. The percentage of patients who achieved and maintained a T level < 20 ng/dL should also be included as a secondary endpoint and included in labeling. The results of patient-reported outcomes can also be included as secondary endpoints, but sponsors should discuss selecting these assessments and their measurement with the division.

7. Statistical Considerations

The primary analysis for the single-arm trial described above should be the calculation of the Kaplan-Meier estimate of the proportion of patients who achieve and maintain castrate T levels (T level < 50 ng/dL) from Day 28 through the end of the treatment period. To demonstrate efficacy, the lower bound of the 95% confidence interval for this estimate should be greater than 90% (i.e., less than 10% *treatment failures*).

For this analysis, a treatment failure is a noncastrate T level (i.e., T level ≥ 50 ng/dL) at any time from Day 28 through the end of the treatment period. This definition of treatment failure combines, therefore, those patients who fail to achieve a castrate T level by Day 28 with those patients who successfully achieve a castrate T level by Day 28 but fail to maintain it throughout the treatment period. Noncastrate T levels prior to Day 28 are not considered treatment failures.

The following censoring rules should be applied for this analysis:

- Patients who leave the trial for reasons other than a noncastrate T level should be censored at their last T level assessment.

- Patients with one or more consecutive missing T levels and a noncastrate T level after the missing time point should be considered to have had a treatment failure at the first missing time point.

- Patients with castrate T levels immediately before and after a single missing T level should not be considered to have had a treatment failure at the missing time point.

- Patients with two or more consecutive missing T levels and castrate T levels immediately before and after the missing time points should be censored at their last T level before the missing data.

Sponsors should conduct a sensitivity analysis in which patients who leave the trial and patients with two or more consecutive missing T levels, regardless of T levels before and after those missing time points, should be considered to have had treatment failures. An additional analysis should exclude patients who received concomitant medications and herbal supplements that could possibly affect T levels.

In determining the sample size of the trial, sponsors should anticipate and account for the possibility of patients leaving the trial prematurely. Every effort should be made to avoid missing data.

D. Labeling Considerations

The Clinical Studies section of labeling should provide information on the percentage of patients who achieved and maintained a castrate (< 50 ng/dL) T level, which is the standard for establishing effectiveness of these products. Labeling should also include the percentage of patients who achieved and maintained a T level < 20 ng/dL during the treatment period. Additionally, to provide information regarding the time course of achieving castrate T levels, the Clinical Studies section may provide data on the percentage of patients treated with GnRH antagonists who achieve castrate levels at Day 14 or 21. Presenting mean T levels over time can be misleading because the mean value may mask a clinically important incidence of treatment failures; therefore, mean T levels should not be included in product labeling.

APPENDIX

The following are general comments regarding the in vitro drug-release method development, acceptance criteria, and data submission that should be provided in the new drug application.

1. In Vitro Drug-Release Method Development Report

a. Provide a detailed description of the in vitro drug-release method being proposed to evaluate the drug product. Provide data to support that the selected in vitro drug-release method development parameters are the most appropriate for the proposed in vitro drug-release method (e.g., testing apparatus, dialysis chamber, in vitro release medium conditions, temperature, etc.). An accelerated drug-release method can be developed for quality control purposes. The testing conditions used for each test should be clearly specified. The release profile should demonstrate complete drug release or a plateau (i.e., no increase over three consecutive time points). We recommend the use of at least 6 samples per testing variable during method development.

b. Provide complete in vitro drug-release profile data (individual, mean, standard deviation) should be provided. The data should be reported as the cumulative percentage of drug released with time (the percentage is based on the product's proposed labeling claim at different time points).

c. Submit data to support the discriminating ability of the selected in vitro drug-release method. In general, the testing should compare the in vitro drug-release profiles of the target product and test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes and process parameters (i.e., ±10% to 20% change to the specification ranges of these variables).

d. Provide supportive validation data for the in vitro drug-release method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

e. Provide a list of critical material attributes and critical process parameters affecting in vitro drug release.

2. In Vitro Drug-Release Acceptance Criteria

The complete in vitro drug-release profile data (e.g., 0.5, 1, and 6 hours, then 1, 2, 4, and 6 days, etc., n = 12) from clinical and registration/stability batches should be used for setting the in vitro drug-release acceptance criteria. A minimum of three time points is recommended to set the acceptance criteria (i.e., sampling time points and acceptance limits) for extended drug-release products from the lots used in the clinical trials and primary stability batches. These time points should cover the early, middle, and late stages of the drug-release profile. The last time point should be where at least 80% of the drug is released. If the maximum amount released is less than 80%, the last time point should be the time when the plateau of the drug-release profile has been reached. In general, the selection of the drug-release acceptance criteria ranges is based on mean target value ±10% and >80% for the last sampling time point. Wider criteria ranges may be

acceptable if they are supported by an approved in vitro–in vivo correlation or physiologically based pharmacokinetic model.

3. Data Submission

The complete in vitro drug-release profile data for the clinical and stability batches of the drug product should be presented in tabular and graphical formats. The tables and plots of mean and individual vessel data for the clinical and stability batches should include profile data at release (time-zero) and throughout the duration of stability testing under long-term storage conditions.