Acromegaly: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Naomi Lowy at 301-796-0692.

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

January 2023
Clinical

Acromegaly: Developing Drugs for Treatment

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

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

January 2023
Clinical

TABLE OF CONTENTS

Acromegaly: Developing Drugs for Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 provide recommendations to sponsors regarding clinical development of drugs for the treatment of patients with acromegaly. This draft guidance is intended to serve as a focus for continued discussions among the Division of General Endocrinology, pharmaceutical sponsors, the academic community, and the public.[2]

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

Acromegaly is a chronic, rare disease in adults (50 to 70 people per million worldwide) caused by excess growth hormone (GH).[3] The most common etiology is a GH-secreting pituitary adenoma that stimulates hepatic overproduction of insulin-like growth factor-1 (IGF-1). Signs and symptoms of acromegaly are caused by the adenoma compressing the surrounding structures (e.g., headaches, vision loss) and by the chronic overproduction of both GH and IGF-1 (bone and tissue overgrowth, diabetes, hypertension, fatigue, weakness, excessive perspiration, joint pain, edema, sleep apnea, and excessive snoring.)

Gigantism occurs with excessive growth hormone secretion in children. Because the manifestations of the disease are different, gigantism is not addressed in this guidance. Under

[1] This guidance has been prepared by the Division of General Endocrinology in the Center for Drug Evaluation and Research at the Food and Drug Administration (the division).

[2] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs for the treatment of acromegaly.

[3] Melmed S, 2006, Acromegaly, N Engl J Med, 355(24):2558–2573.

certain circumstances, development of drugs for acromegaly may trigger the Pediatric Research Equity Act, and, if so, pediatric requirements may apply.[4]

First-line therapy for acromegaly is tumor resection, typically by transsphenoidal surgery. Second-line therapy includes stereotactic radiotherapy and medications that reduce IGF-1 secretion. Guidelines from professional societies[5,6] include recommendations for medical therapy for the following patients with acromegaly: those with persistent or recurrent disease despite surgery, those who are waiting for administered radiotherapy to effectively lower IGF-1 levels (which can take years), and those who are not candidates for surgery or radiotherapy because of poor health.

The goal of medical therapy is to normalize IGF-1 levels for age and sex and to decrease random GH levels below 1 mcg/L. Spontaneous remission of disease occurs occasionally; therefore, in patients who are biochemically controlled, periodic withdrawal of pharmacological treatment is recommended to assess whether the disease remains active in the absence of treatment.[5,7]

Drugs from several pharmacological classes are approved to treat acromegaly, including somatostatin analogs (octreotide, lanreotide, and pasireotide), a GH-receptor antagonist (pegvisomant), and a dopamine-receptor agonist (bromocriptine).

Historically, approved indications reflect two distinct clinical scenarios: 1) patients with uncontrolled disease who are treatment-naive or nonresponders to previous medical treatments (referred to as *treatment of acromegaly* in this guidance) and 2) patients whose disease is controlled on medical therapy and are switching to a different drug (referred to as *maintenance of treatment* in this guidance). To support approval of each indication, the appropriate populations should be included in distinct adequate and well-controlled investigations.

III. DEVELOPMENT PROGRAM

A. General Considerations

- The following are the overall objectives of the clinical development program for drugs intended for the treatment of acromegaly and for maintenance of treatment indications:

[4] See section 505B(a)(1)(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355c(a)(1)(A)).

[5] Katznelson L, ER Laws Jr, S Melmed, ME Molitch, MH Murad, A Utz, and JAH Wass, 2014, Acromegaly: An Endocrine Society Clinical Practice Guideline, JCEM, 99(11):3933–3951.

[6] Giustina A, P Chanson, D Kleinberg, MD Bronstein, DR Clemmons, A Klibanski, AJ van der Lely, CJ Strasburger, SW Lamberts, KKY Ho, FF Casanueva, and S Melmed, 2014, Expert Consensus Document: A Consensus on the Medical Treatment of Acromegaly, Nat Rev Endocrinol, 10(4):243–248.

[7] The Sandostatin LAR Depot labeling recommends yearly withdrawal to assess the disease activity in patients who received pituitary radiation.

- Determine the pharmacokinetics (PK) and pharmacodynamics (PD) of the product in subjects with acromegaly

- Evaluate the relationship between doses and/or exposure-response based on IGF-1 levels in early phase studies to support dose selection for phase 3 pivotal studies

- Establish the efficacy and safety of the drug in subjects with acromegaly

- Selection of the dose or doses and dosing regimen for evaluation in the phase 3 study should be based on the results of the dose-response (IGF-1), pharmacokinetics and pharmacodynamics, and available efficacy and safety information obtained from a phase 2 study. Refer to the draft guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003)[8] and the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration* (November 1994).[9]

  - The selection of doses (starting and incremental doses or fixed doses) for phase 3 studies should be based on either normalization of IGF-1 levels demonstrated in a phase 2 study or decreases in IGF-1 levels that are expected to produce normalization of IGF-1 levels with longer treatment in phase 3 studies. The study duration should account for the drug's half-life, time to achieve steady state, and PD half-life so that the effects of the drug on IGF-1 changes can be accurately assessed.

- Other clinical pharmacological studies, including assessment of drug interactions[10] and the impact of intrinsic and extrinsic factors on the pharmacokinetics and pharmacodynamics of the investigational product, should be conducted early in drug development to aid in the study design of later phase trials.

- In acromegaly drug development programs, substantial evidence of effectiveness has been established with either two adequate and well-controlled trials or one adequate and well-controlled trial with confirmatory evidence. Refer to the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological*

[8] 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.

[9] We update guidances periodically. 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.

[10] See the guidances for industry *In Vitro Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) and *Clinical Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) and the draft guidances for industry *Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications* (November 2020), *Clinical Drug Interaction Studies With Combined Oral Contraceptives* (November 2020) and *Drug-Drug Interaction Assessment for Therapeutic Proteins* (August 2020). When final, these guidances will represent the FDA's current thinking on these topics.

Products (December 2019)[11] for more information about establishing substantial evidence of effectiveness.

  - The phase 3 trial should be randomized and double-blinded and use placebo or an active control. Even though IGF-1 is an objective measure, an open-label design can affect the conduct of the study (e.g., enrollment and/or retention of subjects) and can limit interpretation of safety data. An extension phase should follow to obtain long-term safety data.

- Sponsors should consider the need for washout periods to minimize the residual effects of previous drugs on IGF-1 levels and to confirm persistent disease activity. Duration of washout periods should be drug-specific and based on the relevant drugs' half-lives. Sponsors may propose a shorter washout period with appropriate justification. Factors to consider when deciding on the need for and duration of the washout period include the objectives of the trial, biological half-lives of prior therapies, and the primary efficacy time point. In addition, sponsors should consider how safety will be assessed if a complete washout is not proposed.

  - Sponsors proposing a shorter washout period should acknowledge within the protocol and informed consent the potential increased risk of adverse events because of residual drug activity in the early portion of the trial, and sponsors should include appropriate close monitoring and risk mitigation plans.

- Given that acromegaly is a chronic disease, the safety database should include a sufficient number of subjects with acromegaly treated with the proposed product for at least 12 months, including 6 months of controlled data.

B. Phase 3 Trial Design Considerations

- Placebo-controlled trials have been conducted to support approval of drugs to treat acromegaly. From an ethical perspective, this design is acceptable because treatment guidelines include the recommendation of periodic withdrawal of previous therapies, including subjects who require the lowest doses.[12] In addition, monitoring and timely control of acromegaly-related comorbidities during the trial (e.g., with antidiabetic, antihypertensive medications) and other protocol safeguards (e.g., inclusion/exclusion criteria, rescue criteria) can ensure the safety of subjects while receiving placebo.

- If an active-controlled trial uses a non-US-approved comparator, data should be provided to justify the scientific relevance of the comparative data. In such cases, sponsors should consult the review division regarding their approach.

- If the test drug and comparator have different routes of administration or different regimens, the sponsor should consider a double-dummy trial design. FDA recognizes

[11] When final, this guidance will represent the FDA's current thinking on this topic.

[12] See footnote 5.

blinding may be a challenge in these situations and recommends sponsors consider using placebo if a double-dummy trial design is not feasible.

- For clinical trials, disease control has been defined by biochemical control of IGF-1 levels. Most symptoms of acromegaly are nonspecific, so a normal IGF-1 level in the presence of persistent symptoms has been considered controlled disease.

- The randomized phase of the study should be at least 6 months in duration to allow sufficient time to titrate to an effective dose while minimizing dose-related adverse reactions and to demonstrate the maintenance of IGF-1 levels on the effective dose.

- All phase 3 studies should generally include a titration period and a fixed-dose period that takes into account the drug's half-life and time to reach steady state.

  - The dose or doses of drug should not be increased during the fixed-dose period to better evaluate the durability of the effect of the drug.

  - All dose titrations during the trial should be based on IGF-1 levels with the goal to maintain IGF-1 within the normal reference range.

  - Intervals between up-titrations should be defined by PK parameters, including half-life and time to reach steady state.

  - The dose should be down-titrated any time during the trial based on safety and tolerability of the drug.

  - Symptoms should not be used to guide dose up-titration during the study or studies, given that symptoms are nonspecific.

- For periodic measurements intended to assess the need for dose-titration, a single IGF-1 measurement is acceptable.

- Rescue criteria should be clearly defined in the protocol, and for rescue a subject should meet both clinical and biochemical criteria. Biochemical criteria should define an IGF-1 rescue threshold (e.g., IGF-1 > 1.3x upper limit of normal (ULN)). Clinical criteria can be based on symptoms or signs of worsening disease activity (e.g., worsening diaphoresis, fatigue, soft tissue swelling, hyperglycemia, hypertension).

- Subjects whose disease activity cannot be controlled during the study while using the maximum dose of the study drug(s) should be rescued with approved, effective standard of care therapies. Subjects should not be terminated from trial data collection. They should continue to be followed until the final visit.

C. Phase 3 Eligibility Considerations

- Clinical trials should target patients who would be recommended to receive medical therapy. These typically would include adults with confirmed active acromegaly who had an inadequate response to surgery and/or for whom surgery is not an option.

- Diagnosis of active acromegaly should be confirmed by historically documented evidence of a GH-secreting pituitary tumor based on magnetic resonance imaging and/or pathology report and documented evidence of IGF-1 serum levels above ULN and lack of suppression of GH to < 1 mcg/L following documented hyperglycemia during an oral glucose load.

- For a *treatment of acromegaly* indication, subjects should have uncontrolled disease at baseline, defined as elevated IGF-1 levels above the ULN in those who are treatment-naive or those who were treated with other medical therapies for at least 6 months in the past and did not respond to the maximum dose or did not tolerate the previously used drug.

  - The elevated IGF-1 level should be based on two values obtained during screening 1 to 2 weeks apart. One of the samples should be collected as close to randomization visit as possible (e.g., 1 to 2 weeks).

- For *a maintenance of treatment indication*, subjects should have controlled disease while being treated with stable doses of other acromegaly drug(s) for an appropriate period of time based on the drug's half-life and steady state. Eligible subjects should have documented evidence of active acromegaly because not all patients who have normal IGF-1 while taking medical therapy necessarily have active disease. Continued disease activity can be confirmed by documentation of elevated IGF-1 levels within 1 year before enrollment or by withdrawal of drug therapy before randomization.

  - For a maintenance indication, disease control is defined as an average IGF-1 within the normal range calculated from two assessments 1 to 2 weeks apart during the screening period. Subjects should be on treatment with stable doses of previous drugs until screening. Prior disease activity should be documented in each subject's case report form or patient chart and be available for FDA review.

- Subjects with concomitant conditions that are commonly associated with acromegaly (e.g., cardiovascular disease and diabetes) and older adults should be considered for the phase 3 program to help ensure that the study population better reflects the patient population likely to use the drug in clinical practice. Refer to the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

- Subjects should be excluded if they:

240 – Had pituitary surgery within 6 months of enrollment or received radiation treatment
241 within 5 years of enrollment. The effect of these treatment modalities may be delayed
242 and confound efficacy results.
243
244 – Have pituitary tumors near the optic chiasm. This is to avoid the risk of tumor
245 expansion and compression of optic nerves during treatment.
246
247 • Children under 17 years of age should not be included in the clinical development
248 program for acromegaly because GH over-secretion has a different clinical presentation
249 in this population (i.e., excessive growth or gigantism).
250
251 • Because medical treatment of acromegaly during pregnancy is generally not
252 recommended, pregnant women have not been included in clinical development
253 programs.[13] Enrollment of lactating women can be considered if the available safety data
254 support their inclusion.
255
256 **D. Phase 3 Efficacy Endpoint Considerations**
257
258 • An average of two IGF-1 levels, generally within 1 to 2 weeks, should be obtained to
259 confirm eligibility before randomization may be used as the baseline value.
260
261 • The primary efficacy endpoint to support an acromegaly indication should be
262 normalization of IGF-1 levels after at least 6 months of randomized therapy.
263 Normalization of IGF-1 levels translates into improved signs and symptoms of the
264 disease and ultimately decreases morbidity and mortality associated with acromegaly.
265
266 • Although a decrease in GH levels to < 1 mcg/L also correlates with control of
267 acromegaly, natural secretion of GH is pulsatile, leading to wide variations in plasma GH
268 levels during the day. As such, a single GH value is not reliable in defining disease
269 control, and collecting multiple samples during the day is time-consuming and
270 inconvenient for subjects. GH levels can be evaluated as a secondary endpoint in support
271 of the primary endpoint. These should be collected as multiple samples over 24 hours and
272 averaged.
273
274 • Both GH and IGF-1 should be measured by the program's central laboratory.
275
276 • FDA recommends a responder analysis for the primary efficacy endpoint.
277
278 – For a treatment indication, a responder is a subject with elevated IGF-1 levels at
279 baseline who achieved normal IGF-1 levels at the end of the study and did not require
280 a dose increase during the fixed-dose period.
281

[13] See footnote 5.

- For a maintenance indication, a responder is a subject with normal IGF-1 levels at screening and who has normal IGF-1 levels at the end of the study and did not require a dose increase during the fixed-dose period.

- Subjects who required an increase in dose during the fixed-dose period or who did not have IGF-1 evaluation at the end of the treatment for any reason (missed samples, withdrawn earlier, etc.) should generally be considered as nonresponders in the primary analysis.

- All IGF-1 and GH levels should be obtained at C_{trough}, before the administration of the next dose.

- For the primary efficacy assessment, IGF-1 should be based on an average IGF-1 level of the last two available measurements (within 1 to 2 weeks of each other) at the end of the fixed-dose treatment period. Missing data raises issues of data quality and may interfere with analysis and interpretation of study results. When one of the two last IGF-1 measurements is missing but the subject has not been discontinued from the study, a single value can be used for the study final assessment. However, FDA expects this to occur as an exception and strongly encourages sponsors to collect two values for the study final assessment. A significant amount of missing data can raise questions about data quality.

- Many acromegaly symptoms are nonspecific (e.g., headache, fatigue, sweating) and may be related to concomitant medical conditions (e.g., hypertension, diabetes) or medications. These factors may make it challenging to show that the drug improves symptoms. If a sponsor wishes to show improvement of symptoms, we recommend using fit-for-purpose, patient-reported outcomes that assess the signs and symptoms of acromegaly as key secondary endpoints.[14] Nonvalidated patient-reported outcomes should not be included as primary or key secondary efficacy endpoints and are appropriate as exploratory endpoints only.

E. Phase 3 Statistical Considerations

- Study protocols and statistical analysis plans should clearly prespecify the estimands of primary interest. The description of the estimands should reflect the clinical questions of interest with respect to intercurrent events.[15] The statistical analyses should be aligned with the estimands of primary interest and clearly specify how the sponsor will account

[14] See the draft guidance for industry, FDA staff, and other stakeholders *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments* (June 2022). When final, this guidance will represent the FDA's current thinking on this topic.

[15] Intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest, for example, discontinuation of assigned treatment, use of prohibited medications, use of alternative or additional medications, and corrective surgery. See ICH E9(R1).

for intercurrent events and missing data.[16] Sponsors should consult with FDA regarding these issues during the trial design stage. Sponsors should provide adequate justification that the proposed estimands address meaningful clinical questions of interest and can be estimated with plausible assumptions. Refer to the ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021) for more discussion on estimands and intercurrent events.

- If a noninferiority trial design is considered, the choice of the active control and noninferiority margin should be discussed with the review division. Adequate justification of the noninferiority margin should be provided in the protocol and agreed upon by FDA.

- Subjects should be stratified by history of radiation therapy and severity of the disease at baseline (based on IGF-1 levels at baseline or previous IGF-1 levels).

- Subjects who receive rescue therapy for any reason should not be discontinued from the trial but rather should continue trial participation and follow all planned visits and assessments until the end of the trial.

- Missing data are measurements that were planned to be collected and used for estimating a target estimand but were not available at the end of study. The existence of missing data increases uncertainty in estimation. The amount of missing data should be minimized. Refer to the National Research Council report on missing data for operational measures to prevent missing data.[17]

- Despite the best precautions, some data will inevitably be missing. How the statistical analyses will account for missing data should be prespecified in the statistical analysis plan. Missing data should be imputed in a fashion consistent with what the values would likely have been had they been collected, with the corresponding uncertainty. We generally recommend that missing data be multiply imputed using appropriate methods based on plausible assumptions. Multiple imputations may be aggregated using Rubin's method. For noninferiority comparisons, an imputation under the noninferiority null approach should be considered.

- The imputation of missing data typically relies on assumptions that may not be verifiable. To assess the sensitivity of results to such uncertainty, sensitivity analyses such as tipping point analyses should be conducted that vary assumptions about the missing data. The tipping point analyses should allow assumptions about the missing outcomes on the two treatment arms to vary independently and should also include scenarios where missing data on one treatment indicates worse outcomes than missing data on the other treatment. The goal is to evaluate the plausibility of the assumed expected values for missing

[16] Missing data consist of withdrawal of informed consent for collection of additional data, missed clinical visits, and loss to follow-up.

[17] National Research Council, 2010, The Prevention and Treatment of Missing Data in Clinical Trials, Washington, DC: The National Academies Press.

outcomes on each treatment arm under which the conclusions change (i.e., under which there is no longer evidence of a treatment effect). For continuous data, we recommend performing the tipping point analysis by adding a sequence of constant values ranging from negative to positive numbers to the imputed values from the analysis that most appropriately addresses missing data.

- The number of subjects in confirmatory trials should provide adequate power (e.g., 80 percent) to evaluate the primary endpoint.

- The primary analysis model should estimate the difference and its associated confidence intervals in rate of responders between treatment groups and should incorporate as factors prognostic covariates as well as any variables used to stratify the randomization.

- If statistical significance is achieved on the primary endpoint, the type I error rate should be controlled across all clinically relevant secondary efficacy endpoints intended for product labeling.

- Graphical methods showing IGF-1 values over time should be presented, and additional graphical presentations of the data to illustrate the effect of the drug are encouraged. For example, see the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006).

F. Safety Considerations

Clinical safety assessments should include pituitary tumor size monitoring; injection site reactions, if applicable; evaluation of hypersensitivity reactions as an adverse event of special interest if the investigational product is associated with development of antidrug antibodies; and other adverse events of interest based on the drug's pharmacology, toxicology, or known class effects (e.g., gastrointestinal adverse events, cholelithiasis, blood glucose abnormalities, cardiac function abnormalities).