Endogenous Cushing's Syndrome: Developing Drugs for Treatment

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DRAFT GUIDANCE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)

September 2023
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 provide recommendations to sponsors regarding clinical trial designs for drugs and biologics[2] intended for the treatment of adults with endogenous Cushing's syndrome for whom surgery is not an option or has not been curative. This guidance does not address development of drugs and biologics for the treatment of exogenous Cushing's syndrome. This guidance is intended to focus continued discussions among FDA's Division of General Endocrinology, pharmaceutical sponsors, the academic community, and the public.[3] This is the first guidance drafted by FDA on this topic.

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

Endogenous Cushing's syndrome is a rare condition in which there is production of inappropriately high levels of circulating glucocorticoids from the adrenal gland for a prolonged

[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.

[2] For the purposes of this guidance, all references to *drugs* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and therapeutic biological products licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) that are regulated as drugs.

[3] In addition to consulting guidances, sponsors are encouraged to contact the Division of General Endocrinology to discuss specific issues that arise during the development of drugs for the treatment of endogenous Cushing's syndrome.

period. The estimated annual incidence in the United States is 49 cases per million per year.[4]

Endogenous Cushing's syndrome includes adrenocorticotropic hormone (ACTH)-dependent and ACTH-independent subtypes. Most cases of Cushing's syndrome (80%) are ACTH-dependent and are caused by oversecretion of ACTH. Etiologies of the ACTH-dependent subtype include a pituitary adenoma (Cushing's disease); ectopic ACTH secretion from an ACTH-producing tumor; and, rarely, ectopic corticotropin-releasing hormone (CRH) secretion from a CRH-producing tumor. The less common ACTH-independent subtype is caused by autonomous oversecretion of glucocorticoids by the adrenal gland. Etiologies include an adrenal adenoma, adrenal carcinoma, macronodular adrenal hyperplasia, and primary pigmented nodular adrenal disease.

Cushing's syndrome is characterized by systemic symptoms of hypercortisolism such as easy bruising, facial plethora, proximal myopathy, striae, fatigue, depression, decreased concentration, dorsocervical fat pad hypertrophy, supraclavicular fullness, facial fullness, osteoporosis, peripheral edema, hypokalemia, thin skin, poor skin healing, and metabolic syndrome (hypertension, weight gain, type 2 diabetes mellitus).[5] Cardiovascular complications are the main cause of death for patients with Cushing's syndrome, and the risk of death is independently increased by coexisting diabetes mellitus and/or hypertension.[6]

Recommended first-line treatment of patients with Cushing's syndrome is surgical resection of the primary lesion or lesions.[7] Radiotherapy and/or medical therapy are second-line treatments for patients who have undergone noncurative surgery or who are not surgical candidates. The goal of medical therapy is to control hypercortisolemia either by normalizing cortisol levels (i.e., urinary free cortisol (UFC) ≤upper limit of normal (ULN)) or by blocking the cortisol action at its receptors. Lifelong medical treatment to suppress cortisol levels and/or action may be required if the primary cause of Cushing's syndrome cannot be treated successfully with surgery and/or radiation.

Drugs of different pharmacological classes are approved for the treatment of Cushing's disease and/or Cushing's syndrome or for the treatment of symptoms (e.g., hyperglycemia) associated with Cushing's syndrome. These drugs include somatostatin analogs that inhibit pituitary ACTH secretion, steroidogenesis inhibitors that act at the level of the adrenal glands, and glucocorticoid receptor blockers.

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[4] Broder MS, Neary MP, Chang E, Cherepanov D, and Ludlam WH, 2015, Incidence of Cushing's Syndrome and Cushing's Disease in Commercially-Insured Patients <65 Years Old in the United States, Pituitary, 18(3):283–289.

[5] Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM, and Montori VM, 2008, The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline, J Clin Endocrinol Metab, 93(5):1526–1540.

[6] Clayton RN, Raskauskiene D, Reulen RC, and Jones PW, 2011, Mortality and Morbidity in Cushing's Disease over 50 Years in Stoke-on-Trent, UK: Audit and Meta-Analysis of Literature, J Clin Endocrinol Metab, 96(3):632–642.

[7] Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, and Tabarin A, 2015, Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 100(8):2807–2831.

III. DEVELOPMENT PROGRAM

A. General Considerations

The following are the overall objectives of a clinical development program for a drug intended for the treatment of Cushing's syndrome: determine the pharmacokinetics and pharmacodynamics of the drug in subjects with Cushing's syndrome, evaluate the dose (and/or exposure)-response relationship to support dose selection for phase 3 pivotal studies, and establish the efficacy and safety of the drug in subjects with Cushing's syndrome.

Selection of the dosing regimen for evaluation in phase 3 should be based on the results of the dose (and/or exposure)-response (the measured response depends on the mechanism of action of the drug and may include reduction in UFC, ACTH, blood glucose, blood pressure), pharmacokinetics, pharmacodynamics, and available efficacy and safety information obtained, typically from a phase 2 trial (refer to the 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)).

Other clinical pharmacology studies, including assessment of drug interactions[9] and the impact of intrinsic and other extrinsic factors on the pharmacokinetics and pharmacodynamics of the investigational drug, should be conducted early in drug development to aid in the trial design of later phase trials.

In Cushing's syndrome drug development programs, approaches to establish substantial evidence of effectiveness include two adequate and well-controlled trials or one adequate and well-controlled trial plus confirmatory evidence.[10] In certain cases, a well-designed and executed phase 2 trial can serve as one of the adequate and well-controlled trials. Refer to the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)[11] for more information about establishing substantial evidence of effectiveness.

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[8] 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.

[9] See the guidances for industry *In Vitro Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020), *Clinical Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020), *Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications* (March 2023), *Clinical Drug Interaction Studies With Combined Oral Contraceptives* (June 2023), and *Drug-Drug Interaction Assessment for Therapeutic Proteins* (June 2023).

[10] See FD&C Act section 505(d) (21 U.S.C. 355(d)). For a drug product to be approved by FDA, a sponsor must provide substantial evidence that the drug has the effect it purports to have under the conditions of use described in the proposed labeling and that the drug's benefits outweigh the risks. Generally, the evidence is derived from adequate and well-controlled clinical studies.

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

Phase 3 trials should be randomized, double-blind, and placebo- or active-controlled. An extension phase of at least 6-month duration should follow to obtain durability of response and long-term safety data.

B. Phase 3 Development Program Considerations

1. Drug Development Population

The phase 3 development program should include subjects with confirmed Cushing's syndrome who are candidates for medical therapy according to current medical practice (i.e., subjects with persistence or recurrence of hypercortisolism despite surgery and/or for whom surgery is not an option).

The proposed indication for the drug should reflect the disease subtypes and endpoints studied in the pivotal phase 3 trials. Because some subtypes of Cushing's syndrome are rare (e.g., ectopic ACTH syndrome, adrenal carcinoma, pituitary carcinoma) and it may be challenging to enroll an adequate number of subjects with those subtypes in a clinical trial, FDA will review all available data obtained in even a limited number of subjects. FDA may also consider how data from a broader Cushing's syndrome clinical trial population may apply to the treatment of rarer subtypes, potentially based on the drug's mechanism of action. For example, sponsors may provide a rationale that data from clinical trials of steroidogenesis inhibitors in subjects with Cushing's disease can support approval of the drug for patients with Cushing's syndrome of other rarer subtypes given that the drug inhibits cortisol synthesis, irrespective of the underlying pathophysiology.

Sponsors should also address how the efficacy or dosage of the drug may be affected by differences in the pathogenesis or manifestations of these subtypes. For example, a higher dosage of the drug may be needed to treat higher cortisol levels associated with more aggressive subtypes of Cushing's syndrome (e.g., ectopic ACTH secretion). If there is adequate justification to support the applicability of these data to patients with rare subtypes, this approach may obviate the need for inclusion of many of those subjects in a clinical trial. To best support a broader proposed indication (e.g., in more Cushing's syndrome subtypes), however, sponsors should make every attempt to include as many subjects with the rarer subtypes as possible.

2. Inclusion Criteria

For trials of drugs that either decrease cortisol levels or block the action of cortisol, FDA recommends the following inclusion criteria, at a minimum:

- Subjects who have persistent or recurrent hypercortisolism because of endogenous Cushing's syndrome more than 6 weeks after surgery and/or who are not candidates for surgery or refuse to undergo surgery

- Cushing's syndrome confirmed by the presence of the following:

- UFC above ULN from a minimum of two adequate urinary collections (i.e., adequate urinary volume and creatinine clearance) collected at least 1 week apart. FDA recommends sponsors use threshold of ≥1.5x ULN for UFC to increase the specificity of the test and exclude subjects with pseudo-Cushing's syndrome.

- In addition to elevated mean UFC, presence of either abnormal dexamethasone suppression test or elevated late-night salivary cortisol.

Sponsors should consider the need for adequate washout periods primarily to address and minimize the residual effects of previous drugs on UFC levels. Duration of washout periods should be drug-specific and based on the relevant drugs' half-lives.

For trials of drugs that block cortisol receptors and/or cortisol action but do not decrease cortisol levels, FDA recommends the following inclusion criteria, at a minimum: subjects with glucocorticoid-induced diabetes, glucocorticoid-induced impaired glucose tolerance, or glucocorticoid-induced hypertension at baseline. Because serum cortisol levels are not reliable for assessing the effect of drugs that block cortisol receptors and/or cortisol action at its receptors, the effect of the drug on downstream effects of cortisol, such as hyperglycemia and/or hypertension, should be assessed. The appropriateness and clinical meaningfulness of other endpoints should be discussed with FDA.

3. Exclusion Criteria

For trials of drugs that either decrease cortisol levels or block the action of cortisol, FDA recommends the following exclusion criteria, at a minimum:

- Subjects who have undergone surgery to treat Cushing's syndrome within 6 weeks before screening.

- Subjects who received pituitary radiation therapy within 3 years of screening.

- Subjects without overt Cushing's syndrome, including those with autonomous cortisol secretion,[12] pseudo-Cushing's, or cyclic Cushing's syndrome. To exclude subjects with cyclic Cushing's syndrome, sponsors should document UFC ≥1.5x ULN from at least two urinary collections obtained at least 1 week apart.

For trials of drugs that block cortisol receptors and/or cortisol action but do not decrease cortisol levels (therefore endpoints include glucose- and blood pressure-related parameters), sponsors should consider excluding subjects with a long-standing history (before Cushing's diagnosis) of type 1 or type 2 diabetes or preexisting diabetes, preexisting impaired glucose tolerance, or preexisting hypertension, to optimally avoid confounding effects.

[12] Aron D, Terzolo M, and Cawood TJ, 2012, Adrenal Incidentalomas, Best Pract Res Clin Endocrinol Metab, 26(1):69–82.

4. Choice of Comparator

Placebo-controlled trials have been conducted to support approval of drugs for the indication of both Cushing's syndrome and Cushing's disease. Although some stakeholders have raised concerns about the ethics of a placebo control, this design is regarded as acceptable because monitoring and timely control of Cushing's syndrome–related comorbidities during the trial (e.g., with antidiabetic drugs and antihypertensive drugs) and other protocol safeguards (e.g., inclusion and exclusion criteria, withdrawal criteria) can ensure the safety of subjects. Limitation of the trial duration in a placebo-controlled trial can minimize other disease-related impacts, including osteoporosis, infection, and muscle loss.

Active-controlled trials should use a U.S.-approved drug as a comparator, dosed according to the recommended dosage in FDA-approved labeling, and titrated, as tolerated, to the maximum recommended approved dosage in subjects who do not adequately respond to the lower dosages. If the test drug and comparator have different routes of administration or different regimens, sponsors should consider a double-dummy trial design in order to yield interpretable efficacy and safety data.

5. Efficacy Endpoints

The choice of efficacy endpoints should reflect the drug's mechanism of action. UFC is a reliable marker to assess the efficacy of drugs that inhibit either pituitary ACTH secretion or adrenal steroidogenesis. In contrast, UFC is not a reliable biomarker for drugs that block cortisol receptors. Efficacy for this class of drugs should be established by assessing their impact on downstream effects of cortisol at the glucocorticoid receptor.

<u>For drugs that decrease cortisol levels/inhibit cortisol synthesis:</u>

FDA accepts as a primary efficacy endpoint the sustained normalization of mean UFC levels (i.e., UFC ≤ULN) after a titration phase followed by a fixed-dose period of adequate duration. Treatment guidelines[13] recommend normalization of UFC as the goal of therapy because normalization is associated with reduced morbidity and mortality. Furthermore, UFC is an objective endpoint and is supported by clear mechanistic rationale. All currently marketed drugs that decrease cortisol levels in patients with Cushing's syndrome were approved based on the biochemical control of the disease, (i.e., normalization of UFC levels).

The primary efficacy analysis should be a responder analysis, in which a responder is a subject with elevated UFC levels at baseline who achieved normal UFC levels at the end of the trial. Absolute change in UFC levels from baseline to end of treatment is not a meaningful endpoint because there is lack of consensus on what constitutes an important change from baseline in UFC levels. Rather, per treatment guidelines, normalization of UFC is indicative of disease control. Because UFC levels can fluctuate in patients with Cushing's syndrome, mean UFC levels from a minimum of two adequate urinary collections at both baseline and endpoint should be used for the primary efficacy analysis. Subjects who required a dose increase during the fixed-dose

[13] See the Treatment of Cushing's Syndrome Guideline Resources web page, available at https://www.endocrine.org/clinical-practice-guidelines/treatment-of-cushing-syndrome#1.

period, required rescue therapy, or did not have a final UFC evaluation for any reason (e.g., missed samples, premature withdrawal) should be considered nonresponders in the primary analysis.

For drugs that block glucocorticoid receptors and/or cortisol action but do not decrease cortisol levels:

The primary efficacy endpoint should reflect a downstream effect of cortisol action at the glucocorticoid receptor. FDA recommends using primary efficacy endpoints that reflect cortisol action, for example: glycemic control for subjects who have glucocorticoid-induced type 2 diabetes or impaired glucose tolerance at baseline and/or change in blood pressure values for subjects who have glucocorticoid-induced hypertension at baseline. If sponsors plan to use other measures of cortisol action as primary endpoints, FDA recommends that sponsors provide justification to FDA for that plan and seek FDA's agreement before using such measures as primary endpoints.

For subjects with glucocorticoid-induced type 2 diabetes or impaired glucose tolerance at baseline:

Area under the curve for glucose ($AUC_{glucose}$) with an oral glucose tolerance test (oGTT) has been accepted as a laboratory measure to demonstrate an effect of diminished cortisol action that is likely to be associated with clinical benefit because improvement in $AUC_{glucose}$ is a pharmacodynamic marker for cortisol action. $AUC_{glucose}$ is calculated using frequent measurements to minimize variability.

FDA has not accepted changes in a 2-hour oGTT or hemoglobin A1c (A1c) as markers to demonstrate the effect of diminished cortisol action on hyperglycemic control because results of a 2-hour oGTT can be highly variable and therefore unreliable to assess efficacy. Similarly, the clinical significance of an improvement in A1c in subjects with Cushing's syndrome–induced impaired glucose tolerance, but without diabetes, who may have normal A1c at baseline is unknown.

FDA has accepted a responder analysis in which a response is defined as a reduction in $AUC_{glucose}$ by ≥25% from baseline to the end of the treatment period. Subjects who either require an increase in the dose of the investigational drug during the fixed-dose period or rescue therapy with antihyperglycemic drugs, or those with a missing final $AUC_{glucose}$ evaluation for any reason (e.g., missed samples, early withdrawal) should be considered as nonresponders. Analyses considering $AUC_{glucose}$ as a continuous variable should also be performed to facilitate interpretation of the results from the responder analysis.

The effect of the drug on $AUC_{glucose}$ should be supported by data from secondary endpoints, including changes in A1c and antidiabetic medications in subjects with diabetes (e.g., proportion of subjects who initiated new antidiabetic medications or received dose increases in antidiabetic medications, or proportion of subjects who discontinued antidiabetic treatment or had their dose reduced during the trial).

For subjects with glucocorticoid-induced hypertension:

Change in mean systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) from baseline to the end of the treatment period based on ambulatory blood pressure monitoring is an objective laboratory measure to demonstrate an effect of diminished cortisol action in subjects with glucocorticoid-induced hypertension. To evaluate the pressor effects of drugs, FDA has accepted 1) a responder analysis in which a response is defined as ≥5 mmHg reduction in mean SBP and/or DBP without worsening of either and without any modification in antihypertensive medications attributable to worsening hypertension, or 2) a mean decrease in 24-hour average systolic blood pressure. Subjects who require an increase in the dose of the investigational drug during the fixed-dose period, require rescue therapy with antihypertensive drugs, or do not have final ambulatory blood pressure monitoring evaluation for any reason (e.g., missed samples, withdrawn earlier, etc.) should be considered as nonresponders.

The following secondary endpoints should be assessed to support the primary endpoint:

- Mean difference in 24-hour average SBP (if not the primary endpoint), DBP, and heart rate
- Mean difference in daytime and nighttime average SBP, DBP, and heart rate
- Mean difference in SBP, DBP, and heart rate at the end of treatment period
- Proportion of subjects who initiated new or discontinued previous antihypertensive medication during the trial
- Proportion of subjects with dose increases or decreases in antihypertensive medication during the trial

6. Safety Considerations

Because Cushing's syndrome is a chronic disease, the safety database should include a sufficient number of subjects with Cushing's syndrome treated with the proposed drug for at least 12 months (typically approximately 150 subjects). If new safety issues arise in the nonclinical[14] program or during the phase 3 clinical program, FDA may recommend that sponsors conduct additional nonclinical studies or clinical trials and/or trials of longer duration to evaluate the new safety signals.

At a minimum, clinical safety assessments should include monitoring of the following adverse events of special interest:

- Pituitary tumor enlargement in subjects with Cushing's disease

[14] 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 it they wish to use a nonanimal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

- Adrenal insufficiency

  - Serum cortisol levels may be needed to differentiate adrenal insufficiency from cortisol withdrawal syndrome in trials evaluating drugs that inhibit cortisol synthesis. Serum cortisol levels < 5.4 g/dl are diagnostic of adrenal insufficiency that is a life-threatening condition and is associated with such serious symptoms as hypotension, electrolyte disturbances, dehydration, loss of consciousness, and ultimately death if left unrecognized and untreated. The treatment is immediate discontinuation of the drug and treatment with glucocorticoids. On the other hand, cortisol withdrawal syndrome is attributable to the fact that most patients with hypercortisolemia poorly tolerate low normal levels of cortisol or rapid decrease in cortisol levels (rather than attributable to low absolute cortisol levels). The signs and symptoms associated with rapid decrease in cortisol levels are similar to symptoms of true adrenal insufficiency (e.g., nausea, vomiting, fatigue); however, rapid cortisol decrease is non-life-threatening because the absolute levels of cortisol remain within normal limits. This condition is usually self-limiting or requires dose decrease/interruption; treatment with glucocorticoids is rarely required. In general, to control hypercortisolemia associated with Cushing's syndrome it is recommended to achieve cortisol levels 5.4-10.8 g/dl.[15]

  - Serum cortisol levels are not reliable for the diagnosis of adrenal insufficiency or cortisol withdrawal syndrome in patients treated with cortisol receptor antagonists. Thus, in trials evaluating cortisol receptor antagonists, sponsors should incorporate appropriate monitoring based on signs and symptoms of adrenal insufficiency as part of their safety evaluation. Sponsors should prespecify in the protocol the signs and symptoms of adrenal insufficiency that may require a dose decrease and/or treatment discontinuation.

  - FDA does not recommend relying on levels of UFC to diagnose adrenal insufficiency or cortisol withdrawal syndrome because of high variability in levels.

  - The protocol should specify criteria for rescue therapy with glucocorticoids and treatment discontinuation or interruption followed by restarting with lower doses.

- For drugs that block cortisol receptors and/or cortisol action at its receptors, symptoms associated with activation of mineralocorticoid receptors (e.g., hyperaldosteronism-like symptoms such as elevated blood pressure, low potassium levels)

[15] Nieman LK, Biller BMK, Findling JW, Murad MH, Newell-Price J, Savage MO, and Tabarin A, 2015, Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline, J Clin Endocrinol Metab, 100(8):2807–2831.

- For cortisol synthesis inhibitors, adverse events associated with potential accumulation of steroid hormone precursors (e.g., 11- deoxycorticosterone, 11-deoxycortisol),[16] including hirsutism, acne, hypokalemia, hypertension, and edema

7. Trial Procedures and Timing of Assessments

- The main phase of phase 3 trials should include a drug titration period to allow titration to achieve normalization of UFC or maximum tolerable dosage followed by a fixed-dose period of sufficient duration during which the doses should not be increased to evaluate efficacy and durability. Sponsors should consider the half-life of the drug and discuss it with FDA when deciding the duration of the fixed-dose period.

  - Depending on the mechanism of action of the drug, the titration period should be long enough to achieve the maximum dosage of the drug needed to either normalize UFC levels or to demonstrate an improvement in glucocorticoid-induced hyperglycemia or hypertension.

  - Dose titration should be based on objective measures (e.g., UFC level for drugs that decrease cortisol secretion; or plasma glucose values, mean 24-hr SBP and/or DBP, etc., for drugs that block glucocorticoid receptors and/or cortisol action but do not decrease cortisol levels) and safety signals (e.g., onset of adrenal insufficiency).

  - Improvement in symptoms should not be used to guide dose up-titration. Symptoms can be nonspecific and may be subject to bias. In addition, resolution of symptoms may be delayed following normalization of cortisol levels.

- For trials of drugs that block cortisol receptors and/or cortisol action but do not decrease cortisol levels, subjects should be assigned at time of randomization to either a glucocorticoid-induced hyperglycemia subgroup or a glucocorticoid-induced hypertension subgroup for the analysis of efficacy endpoints, depending on which abnormality they have at baseline. The protocol should also prespecify whether subjects with concomitant glucocorticoid-induced diabetes/impaired glucose tolerance and hypertension will be assigned to either one or both subgroups, and whether subjects who have improvement in one endpoint and worsening or no improvement in the other endpoint will be classified as responders or nonresponders.

- For UFC measurement in trials of investigational drugs that decrease cortisol levels/inhibit cortisol synthesis, the following are recommended:

  - Baseline assessment: An average of at least two UFC levels obtained within 1 to 2 weeks before randomization should be used for the baseline assessment.

  - Efficacy assessment: UFC level should be based on an average of at least two UFC levels obtained within 1 to 2 weeks at the end of the fixed-dose period. This might

[16] These precursors may reflect the shift of steroidogenesis toward the androgen pathway. Precursors other than adrenal hormonal precursors may accumulate.

lead to missing data, and a single last value can be used for the final trial assessment. However, FDA expects that this will occur only in a minority of subjects, if any. A significant amount of missing data can raise questions about data quality, which may lead to uncertainties about the trial results.

- Dose titration should generally be based on mean UFC values calculated from at least two UFC samples.

- Central laboratory assays should be used for all UFC measurements.

- For the drugs that block cortisol receptors and/or cortisol action but do not decrease cortisol levels, the following are recommended for subjects with glucocorticoid-induced type 2 diabetes or impaired glucose tolerance at baseline:

  - $AUC_{glucose}$ should be calculated based on oGTT values. A 2-hr oGTT should be obtained for all subjects at baseline (i.e., 1 to 2 weeks before randomization) and at regular intervals for subjects who have diabetes or impaired glucose tolerance at baseline. oGTT should be obtained within 1 week of the end of the fixed-dose period for the calculation of $AUC_{glucose}$ for the efficacy assessment.

  - A1c should be obtained for all subjects at baseline (i.e., 1 to 2 weeks before randomization) and then every 3 months.

  - Efficacy assessment (secondary endpoint):

    - Change in A1c in the subgroup of subjects with glucocorticoid-induced diabetes at baseline after at least 3 months of treatment should be included as a secondary endpoint to provide supportive evidence of efficacy of the drug.

    - A1c obtained within 1 week of the end of fixed-dose period should be used for the efficacy assessment.

    - Changes in dose(s) and/or number of antidiabetic medications.

- For the drugs that block cortisol receptors and/or cortisol action but do not decrease cortisol levels, the following are recommended for subjects with glucocorticoid-induced hypertension:

  - SBP and DBP values should be measured by ambulatory blood pressure monitoring.

  - For the baseline assessment, mean SBP and mean DBP should be obtained within 1 to 2 weeks before randomization for all subjects at baseline, followed by regular intervals.

    - For dose titration, mean SBP and/or mean DBP values obtained within 1 week of the titration visit should be used for dose titration.

- For the primary and secondary efficacy endpoints, mean blood pressure obtained within 1 week of the end of the fixed-dose period should be used.

- For the secondary endpoint, changes in dose(s) and/or number of antihypertensive medications.

8. Statistical Considerations

- Trial 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 in respect to thoughtfully envisioned intercurrent events.[17] The statistical analyses should be aligned with the estimands of primary interest and clearly specify how intercurrent events and missing data will be accounted for. Sponsors should consult with FDA about these issues during the trial design stage. Sponsors should provide adequate justifications that the proposed estimands address meaningful clinical questions of interest and can be estimated with plausible assumptions. Refer to ICH E9(R1) for more discussions on estimands and intercurrent events.

- If a noninferiority trial design is considered, sponsors should discuss with FDA the choice of the active control and noninferiority margin. FDA recommends that sponsors provide FDA with adequate justification in the protocol for their choice of noninferiority margin and seek FDA's agreement on that choice.[18]

- Randomization of subjects should be stratified by UFC levels at baseline, country/region, and prior radiation therapy. In addition, in trials of drugs that block cortisol receptors and/or cortisol action but do not decrease cortisol levels, subjects assigned to the glucocorticoid-induced hyperglycemia subgroup should be stratified by diabetes versus impaired glucose tolerance.

- Subjects who initiate rescue therapy for any reason and/or discontinue study treatment should continue trial participation and follow all planned visits and assessments until the end of the trial.

- Missing data are measurements that are planned to be collected and used for estimating a target estimand but not available at the end of the trial. Missing data may occur because of withdrawal of informed consent for collection of additional data, missed clinical visits, and loss to follow-up. The existence of missing data increases uncertainty in estimation.

[17] 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 (e.g., discontinuation of assigned treatment, use of prohibited medications, use of alternative or additional medications, corrective surgery). See the ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

[18] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016) (FDA Noninferiority Guidance).

The amount of missing data should be minimized. For operational measures to prevent missing data, refer to the National Academy of Sciences report on missing data.[19]

- Despite the best precautions, some data will inevitably be missing. How the statistical analyses will account for missing data should be carefully prespecified in the statistical analysis plan. Missing data should be imputed with the corresponding uncertainty in a manner consistent with what the values would likely have been had they been collected. We generally recommend that missing data be multiply imputed using appropriate methods based on plausible assumptions. Rubin's method can be used to combine the estimated treatment effects and variability across the multiple imputations. For noninferiority comparisons, an imputation under the noninferiority null approach should be considered per the FDA Noninferiority Guidance.

- The imputation of missing data typically relies on some assumptions of missing mechanisms that are not verifiable. To assess the sensitivity of results to such uncertainty, sponsors should conduct sensitivity analyses, such as tipping point analyses, 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 arm indicates worse outcomes than missing data on the other treatment arm. The goal is to evaluate the plausibility of the assumed expected values for missing 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 centering the tipping point analysis around the analysis that most appropriately addresses missing data.

- Supplementary analyses targeting different estimands may be useful to provide additional insights into the treatment effect, but they do not directly evaluate the missing data assumptions of the primary analysis.

- The number of subjects in confirmatory trials should provide adequate power 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 adjust for 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 UFC values over time should be presented, and additional graphical presentations of the data to illustrate the effect of the drug are encouraged. For

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

examples, see the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2006).