NDA 219398

CORRECTED COMPLETE RESPONSE

Corcept Therapeutics
Attention: Christopher Golis
Vice President, Quality Assurance & Regulatory Affairs
101 Redwood Shores Parkway
Redwood City, CA 94065

Dear Christopher Golis:

Please refer to your new drug application (NDA) dated and received (b) (4), and your amendments, submitted under (b) (4) for relacorilant capsules.

We also refer to our complete response letter dated December 30, 2025, which contained no errors but is being updated to respond to Concept's communication dated (b) (4).

This corrected action letter incorporates revisions for clarity. The effective action date will remain December 30, 2025, the date of the original letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Clinical and Statistical

1. Substantial evidence of effectiveness

   To support efficacy for the (b) (4), you submitted the results of two phase 3 trials (CORT125134-455[1] and CORT125134-456[2]). For the following reasons, the provided evidence is not sufficient to demonstrate the effectiveness of relacorilant for the proposed indication.

[1] Trial CORT125134-455: Glucocorticoid Receptor Antagonism in the Treatment of Cushing's Syndrome: A Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study of the Efficacy and Safety of Relacorilant
[2] Trial CORT125134-456: Glucocorticoid Receptor Antagonism in the Treatment of Hypercortisolism in Patients with Cortisol-Secreting Adrenal Adenomas or Hyperplasia: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Relacorilant

A. CORT125134-455

CORT125134-455 was conducted in subjects with endogenous Cushing's syndrome and concurrent hypertension (defined as mean systolic blood pressure ≥135 to ≤170 mm Hg and/or mean diastolic blood pressure ≥85 to ≤110 mm Hg, measured by ambulatory blood pressure monitor and no increase in doses of antihypertensive medications for at least 4 weeks prior to baseline assessment) and/or diabetes (DM)/impaired glucose tolerance (IGT). The trial included a 22-week single-arm, open-label treatment phase, which was followed by a 12-week placebo-controlled, randomized withdrawal phase. The primary endpoint of this trial was the loss of response with respect to hypertension from open-label phase Week 22 to randomized-withdrawal phase Week 12, based on 24-hour ambulatory blood pressure monitoring (ABPM), in subjects with baseline hypertension.

While CORT125134-455 met its primary endpoint, the analysis was conducted in a highly enriched population. Of the (b) (4) subjects enrolled, 102 subjects had hypertension at baseline, of which 40 (39%) subjects discontinued the trial during the open-label phase and only 46 (45%) subjects entered the randomized withdrawal phase. As such, the observed treatment effect in the randomized withdrawal phase likely overestimates the treatment effect of relacorilant in the intended population. We acknowledge that in the 22-week open-label period, in which all subjects were treated with relacorilant, the mean (SD) change from baseline in systolic blood pressure at the end of the open-label phase was -5.2 (10.4) mm Hg (with missing data imputed using a return-to-baseline approach). However, we find this treatment estimate to be unreliable given the large amount of missing data. In addition, there was no control group with which to interpret the change in blood pressure.

B. CORT125134-456

CORT125134-456 was a randomized, double-blind, placebo-controlled trial in subjects with Autonomous Cortisol Secretion (ACS) and Cushing's Syndrome, associated with uncontrolled systolic hypertension and/or DM/IGT. However, the trial did not meet its primary efficacy endpoint, defined as the mean change in 24-hour average systolic blood pressure (SBP) based on 24-hour ABPM, from baseline to Week 22 in subjects with systolic hypertension at baseline. In the (b) (4) subjects with ACS and Cushing's Syndrome and with hypertension at baseline ((b) (4) in each arm), the mean change in 24-hour SBP from baseline was -5.8 mmHg in the relacorilant arm and -5 mmHg in the placebo arm, resulting in a between-arm difference (relacorilant vs. placebo) of -0.85 mmHg (95% CI: -6.7, 4.9; p-value 0.77).

We acknowledge that you also conducted a post-hoc analysis of the primary endpoint in the 33 subjects with hypertension and Cushing's Syndrome (16 in

relacorilant arm and 17 in placebo arm). Your analysis showed a nominally significant decrease in systolic blood pressure compared to placebo as follows: the Least Squares mean change from baseline to Week 22 in systolic blood pressure was -11.2 mm Hg in the relacorilant arm, compared to -0.8 mm Hg in the placebo arm, resulting in a nominally significant difference between the two arms of -10.4 mm Hg (95% CI: -19.7, -1.2; nominal p-value 0.03). However, this analysis was not pre-specified in the statistical analysis plan, and in general, post-hoc analyses of a failed trial can be unreliable. Additionally, your analysis was based on a small number of subjects and there was a large amount of missing data (only 8/16 subjects in the relacorilant arm and 13/17 subjects in the placebo arm were included). A wash-out imputation method that we conducted during review of your application failed to demonstrate even nominal statistical significance for the estimated treatment effect of relacorilant compared to placebo in this subgroup. Our results showed that the Least Squares mean change from baseline in 24-hour SBP was -7.7 mm Hg in the relacorilant arm, compared to -2.8 mm Hg in the placebo arm, resulting in a treatment difference between the two arms of -4.9 mm Hg (95% CI: -15.3, 5.6; nominal p-value 0.36).

During the pre-submission meetings, we informed you on several occasions of our concerns about the adequacy of the clinical development program to assess the effect of relacorilant on hypertension in the intended population including the design of CORT125134-455, and to expect significant review issues if you were to submit your application.

2. Benefit Risk Assessment

As substantial evidence of effectiveness was not demonstrated we are unable to conduct a final benefit risk assessment for relacorilant for the proposed indication. After conducting a thorough safety review, we concluded that relacorilant is associated with drug induced liver injury (DILI). While no subjects met the traditional Hy's law criteria for severe DILI, four cases were assessed as probable DILI due to relacorilant, with one subject experiencing a significant alanine aminotransferase (ALT) elevation of 1952 U/L, representing more than 50 times the upper limit of normal. Post-market data indicate that patients with ALT >1000 U/L due to DILI have increased risk for developing jaundice (Hy's law) which carries a higher liver related fatality risk.[3] The temporal relationship of the adverse event to study drug initiation, and the lack of alternative etiology identified despite extensive work-up, suggests this event was likely related to relacorilant treatment. The continued rise in liver enzyme levels after relacorilant discontinuation does not rule out relacorilant as an instigating factor, as drug-induced liver injury can persist for weeks to months after

[3] Chalasani N, et al. Prognostic significance of very high and towering peak alanine aminotransferase (ALT) values with normal or near normal total bilirubin in patients with idiosyncratic drug-induced liver injury. J of Hepatology. 82: Suppl 1, S97-FRI-153. (2025)

the offending drug is discontinued. Because there were only 303 subjects exposed (to at least one dose of relacorilant), identification of DILI cases in even 4 subjects is concerning and it remains possible that more DILI cases may occur in the larger population with longer exposure in post-approval settings.

Based on the currently available information, we cannot conclude that relacorilant has a favorable benefit risk assessment for the proposed indication. We also reviewed the exploratory evidence for benefits aside from (b) (4) such as body weight and blood glucose control and were not persuaded that such benefits were observed in your clinical development program.

Path forward

To address these deficiencies, you will need to provide new clinical data to demonstrate that relacorilant treatment results in a clinically meaningful (b) (4) . In addition, the benefits demonstrated to be attributable to relacorilant must outweigh its risks.

We also recommend that you submit a proposal for adequate DILI risk mitigation strategies including appropriate labeling warnings, routine monitoring requirements, enhanced pharmacovigilance, and post-market evaluation.

Additionally, from a mechanistic standpoint, glucocorticoid receptor antagonism would be expected to improve other aspects of (b) (4) . Although you may continue to focus on (b) (4) only, relacorilant may have benefit for the broader indication of treatment of (b) (4) . If you choose to investigate this hypothesis further, we are open to meeting with you to discuss a feasible controlled clinical trial design using a novel endpoint such as a composite of signs and symptoms of (b) (4) .

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

[4] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[5] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to our correspondence dated, (b) (4), which addresses the proposed proprietary name, (b) (4). This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all of the application deficiencies that have been identified in this letter.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact (b) (4) .

Sincerely,

{See appended electronic signature page}

(b) (4)

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (4)

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