NDA 220707

COMPLETE RESPONSE

Disc Medicine, Inc.
Attention: Steve Caffé, MD
Chief Regulatory Officer
321 Arsenal Street, Suite 101
Watertown, MA 02472

Dear Dr. Caffé:

Please refer to your new drug application (NDA) (b) (4) or bitopertin oral tablets.

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/BIOSTATISTICS

On (b) (4), you submitted NDA 220707 for bitopertin for (b) (4). You seek approval of this application under the provisions of (b) (4), proposing the primary biomarker endpoint of percent change in whole blood metal-free protoporphyrin IX (PPIX) as a surrogate endpoint that is reasonably likely to predict clinical benefit.

In support of approval, you submitted the results of Study DISC-1459-201 (Trial 201) and Study DISC-1459-202 (Trial 202). Trial 201 was a randomized, double-blind, placebo-controlled trial in subjects 18 years of age and older with EPP. The trial included a 28-day screening period and a randomized 120-day treatment period. The trial enrolled (b) (4) subjects, including (b) (4) randomized to bitopertin 20 mg, (b) (4) randomized to bitopertin 60 mg, and (b) (4) randomized to placebo. The trial was conducted at 9 sites in the United States. Trial 202 was a randomized, open-label trial of bitopertin 60 mg vs. 20 mg in subjects 12 years of age and older with EPP or XLP. The trial included a 28-day screening period and a randomized 168-day treatment period. The trial was conducted at 2 sites in Australia. The trial enrolled (b) (4) subjects, including (b) (4) randomized to bitopertin 20 mg and (b) (4) randomized to bitopertin 60 mg. The primary biomarker endpoint was the percent change in whole blood metal-free PPIX levels from baseline to end of the treatment period (Day 121 in Trial 201 and Day 169 in Trial 202). You propose an ongoing trial, DISC-1459-301, as your confirmatory trial.

The approvability of an NDA under the provisions of (b) (4), relies on, in part, two factors: first, whether there is evidence of an effect on the proposed surrogate endpoint; and second, whether the proposed surrogate endpoint, including the magnitude of change, is reasonably likely to predict a clinical benefit.

With respect to the first factor, we agree that Trial 201, one adequate and well-controlled trial, demonstrated an effect on its primary endpoint. In Trial 201, bitopertin 60 mg was superior to placebo for the primary biomarker endpoint of percent change from baseline to Day 121 of whole blood metal-free PPIX in adult patients with EPP ($p<0.001$). Confirmatory evidence was provided from a second, randomized, open-label trial, Trial 202, in which bitopertin 60 mg was superior to bitopertin 20 mg for the primary biomarker endpoint of percent change from baseline to Day 169 of whole blood metal-free PPIX in adult and adolescent patients with EPP or XLP ($p=0.018$).

However, there are uncertainties with respect to the second factor. The percent change in PPIX was relatively modest (about 40% reduction from baseline to Day 121 for the higher 60 mg dose) and whether that magnitude of change in whole blood metal-free PPIX is reasonably likely to predict clinical benefit is unknown. This uncertainty is further exacerbated by the results from Trials 201 and 202 which did not show evidence of association between percent change in whole blood metal-free PPIX and sunlight-exposure based endpoints, as measured in the trials, despite the strong mechanistic and biological plausibility supporting the use of the PPIX biomarker in (b) (4). This lack of correlation between the changes in PPIX and clinical outcomes measured leaves significant uncertainty that bitopertin will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

For this application to be approved, you will need to provide evidence from an adequate and well-controlled trial(s) demonstrating the efficacy of bitopertin for (b) (4) based on clinical endpoint(s). The Division is willing to meet with you to discuss options, such as completing your ongoing trial and, if the trial is successful, submitting the results to support a traditional approval.

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] 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, email (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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