

BLA 761427/Original 2

COMPLETE RESPONSE

LIB Therapeutics, Inc.
Attention: Evan A. Stein, MD, PhD
Chief Executive and Scientific Officer
5375 Medpace Way
Cincinnati, OH 45227

Dear Dr. Stein:

Please refer to your biologics license application (BLA) received (b) (4) for
Lerochol (lerodalcibep-liga) injection.

BLA 761427 provides for the use of Lerochol (lerodalcibep-liga) for the following indications which, for administrative purposes, we have designated as follows:

- BLA 761427/Original 1 - Lerochol is indicated as an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in adults with hypercholesterolemia, including heterozygous familial hypercholesterolemia (HeFH).

- (b) (4)

The subject of this action letter is BLA 761427/Original 2. A separate action letter will be issued for BLA 761427/Original 1.

All future submissions to BLA 761427/Original 1 and BLA 761427/Original 2 should specify the BLA number and the Original number to which each submission pertains.

We have completed the review of BLA 761427/Original 2 as amended and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

The phase 3 trial, Trial 003, in the HoFH population failed to demonstrate efficacy for the proposed indication.

- Trial 003 was a randomized, open-label, cross-over, noninferiority trial that consisted of two 24-week treatment periods separated by an 8-week washout period. The mean LDL-C reduction by intent-to-treat (ITT) analysis at Week 24 was -4.9% when subjects were receiving Lerochol (also referred to as LIB003) and -10.3% when the same subjects were receiving evolocumab. The difference between the two treatments was 5.4%, with a corresponding 95% CI of [-0.2, 11.1]. The upper limit of the 95% CI exceeded the prespecified noninferiority margin of 6%, therefore, the trial did not demonstrate that LIB003 was noninferior to evolocumab. Given concerns for the cross-over design of the trial, an additional analysis of the primary efficacy endpoint for Period A only was performed. The percent change in LDL-C from baseline to Week 24 in Period A was -0.15%, with a corresponding 95% CI of [-11.32, 11.02] for the LIB003-treated subjects compared to -17.9%, with a corresponding 95% CI of [-25.12, -10.77] for evolocumab-treated subjects. The LIB003 group, therefore, did not achieve a clinically significant reduction in LDL-C in Period A.

As a path forward, we recommend that you provide additional data to demonstrate that Lerochol is effective for the proposed indication.

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 Resources¹ and Pregnancy and Lactation Labeling Final Rule² 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.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.³

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

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

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>

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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- (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 patient 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 601.3(b). 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 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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You may request a meeting or teleconference with us to discuss what steps you need to take before BLA 761427/Original 2 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*.⁴

If you have any questions, contact

(b) (4)

Sincerely,

{See appended electronic signature page}

(b) (4)

Center for Drug Evaluation and Research

⁴ 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/RegulatoryInformation/Guidances/default.htm>.

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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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