

BLA 761458/Original 2

COMPLETE RESPONSE

GlaxoSmithKline LLC
Attention: David Colton
Director, Global Regulatory Affairs
200 Cambridge Park Drive
Cambridge, Massachusetts 02140

Dear David Colton:

Please refer to your biologics license application (BLA) received (b) (4) for Exdensur (depemokimab-ulaa) injection.

BLA 761458 provides for the use of Exdensur (depemokimab-ulaa) for the following indications which, for administrative purposes, we have designated as follows:

- BLA 761458/Original 1 - Add-on maintenance treatment of severe asthma characterized by an eosinophilic phenotype in adult and pediatric patients aged 12 years and older

(b) (4)

The subject of this action letter is BLA 761458/Original 2. A separate action letter will be issued for BLA 761458/Original 1.

All future submissions to BLA 761458/Original 2 should specify the BLA number and the Original number to which each submission pertains.

We have completed the review of BLA 761458/Original 2 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/STATISTICAL

The submitted data do not provide adequate evidence to support approval of depemokimab (b) (4)

(b) (4)

Efficacy for depemokimab was evaluated in two, replicate, randomized (1:1), double-blind, placebo-controlled trials (ANCHOR-1 and ANCHOR-2) in n=(b) (4) adults with inadequately controlled CRSwNP. Participants were followed for 52 weeks to assess the co-primary endpoints of change from baseline on endoscopic nasal polyp score and self-reported symptoms on a nasal obstruction mean score. The results from the nasal obstruction score are especially important for assessing benefit-risk because they are a direct reflection of the clinically meaningful effects for patients.

The co-primary endpoints of nasal polyp score and nasal obstruction score were statistically significant in ANCHOR-1 & 2. However, the nasal obstruction scores were not robust to sensitivity analyses for missing data and handling of intercurrent events. In addition to the statistical deficiencies, the effect sizes for both co-primary endpoints were numerically small and, specifically for the nasal obstruction score, of uncertain clinical meaningfulness.

The review team also considered secondary endpoints for evidentiary support, including additional patient reported symptom scores, the need for nasal sinus or polyp surgery, and oral corticosteroid use. Despite trends favoring depemokimab, no secondary endpoint met statistical significance based on the pre-specified hierarchical testing strategy.

The 100 mg dose was selected based on a modeling and simulation approach informed by PK/PD data from the first-in-human single-dose trial in subjects with mild-to-moderate asthma. No phase 2 dose-ranging trials in participants with CRSwNP were conducted. Exposure response analyses of ANCHOR-1 & 2 demonstrated a trend that higher exposure is generally associated with greater placebo-adjusted treatment effects in reduction of total endoscopic nasal polyp score and nasal obstruction score in CRSwNP participants, especially in CRSwNP participants with comorbid asthma. This indicates that a higher dose of depemokimab may provide a greater treatment effect.

While the every 6 month dosing interval has advantages for adherence, non-responders would either have to wait six months to switch to a more effective therapy, or initiate a second biologic therapy while depemokimab is still present systemically, potentially causing an associated increase in risk of dual biologic therapies. Given the small effect size for depemokimab with lack of robustness on tipping point analysis, the benefit-risk in the setting of a six-month duration of action is not favorable.

Information Needed to Resolve the Deficiency

Provide new evidence demonstrating a treatment effect of sufficient magnitude to establish that depemokimab will provide a statistically persuasive and clinically meaningful benefit to patients with CRSwNP.

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

CARTON AND CONTAINER LABELING

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

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.

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>

- 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.

You may request a meeting or teleconference with us to discuss what steps you need to take before BLA 761458/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

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>.
U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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)

12/16/2025 04:19:35 PM