



BLA 761211

**COMPLETE RESPONSE**

Immedica Pharma AB  
% DLRC Inc.  
Attention: Gregory Dombal  
President  
1 Broadway  
Cambridge, MA 02142

Dear Gregory Dombal:

Please refer to your biologics license application (BLA) (b) (4)  
[REDACTED]  
[REDACTED] for AEB1102.

We acknowledge receipt of your major amendment dated (b) (4), which extended the goal date by three months.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We recognize that arginase 1 deficiency (ARG1-D) is a rare and serious disease and that there is high unmet need with no approved therapies.

We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**DEFICIENCIES AND INFORMATION NEEDED TO RESOLVE THE DEFICIENCIES**

(1) Dose adjustment and monitoring of plasma arginine are required for the safe and effective use of AEB1102. (b) (4)

[REDACTED]

(b) (4)  
[REDACTED]

- (2) The effectiveness of AEB1102 has not been established for traditional approval, even when applying regulatory flexibility for this rare and serious disease. The primary evidence of efficacy for AEB1102 was evaluated in a single adequate and well controlled trial (CAEB1102-300A) that included pediatric and adult subjects with ARG1-D. Results showed a statistically significant reduction in plasma arginine levels favoring AEB1102, with an estimated treatment difference of  $-311\mu\text{M}$  (95% CI  $-380, -242$ ,  $p < 0.0001$ ). However, the trial did not achieve either of its key secondary endpoints: 2-minute walk test (2MWT) (treatment difference of 5.5, 95% CI  $(-15.6, 26.7)$ ,  $p = 0.60$ ) and Gross Motor Function Domain part E (GMFM-E) (treatment difference of 4.1, 95% CI  $(-1.5, 9.7)$ ,  $p = 0.14$ ). The related endpoint, Gross Motor Function Domain part D (GMFM-D) had a treatment difference of 3.0 (95% CI: 0.3, 5.7, nominal  $p = 0.03$ ). Thus, while there were trends in improvement in clinical endpoints during the placebo-controlled period of the trial, the results overall did not definitively establish a clinical benefit of AEB1102. In addition, there was no definitive evidence of clinical benefit in other data sources, such as the open label extension as subjects in the placebo group who received AEB1102 starting at Week 24 did not show numerical improvements in the clinical endpoints. While AEB1102 treatment led to statistically significant reductions in plasma arginine, the submitted data are not adequate to support plasma arginine as a validated surrogate endpoint predictive of clinical benefit. However, the additional supportive evidence suggested that plasma arginine may be reasonably likely to predict clinical benefit based on correlations observed in the pivotal trial and a systematic review of case studies.

We recommend that you conduct a trial that assesses clinical outcomes to validate that plasma arginine and/or its metabolites are predictive of clinical benefit. Conceivably, because plasma arginine alone or in combination with specific metabolites may be considered a reasonably likely surrogate endpoint to predict clinical benefit, it may be acceptable that such a trial would be conducted as a postmarketing confirmatory trial if your application was resubmitted via the accelerated approval pathway.<sup>1,2</sup> We welcome dialog to discuss potential designs for such a trial and the possible acceptability of utilizing the accelerated approval pathway for the resubmission of your BLA.

---

<sup>1</sup> For additional information on the accelerated approval pathway and their requisite confirmatory trials, see the FDA draft guidances for industry *Expedited Program for Serious Conditions — Accelerated Approval of Drugs and Biologics*, available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/accelerated-approval-expedited-program-serious-conditions>, and *Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway*, available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/accelerated-approval-and-considerations-determining-whether-confirmatory-trial-underway>.

<sup>2</sup> We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

**PRESCRIBING INFORMATION**

We reserve additional comment on the proposed labeling at this time. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources<sup>3</sup> and Pregnancy and Lactation Labeling Final Rule<sup>4</sup> 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 Prescribing Information 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.<sup>5</sup>

**PROPRIETARY NAME**

Please refer to 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 product 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.

---

<sup>3</sup> <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

<sup>4</sup> <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

<sup>5</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

- 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 product. Include an updated estimate of use for product marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

### **ADDITIONAL COMMENTS**

We have the following comments/recommendations that are not approvability issues:

#### **Clinical**

1. There is a lack of safety and efficacy data in subjects less than 2 years of age and safety concerns related to low arginine levels, especially in younger patients. Therefore, the provided information does not support the proposed inclusion of pediatric patients of all ages. We recommend a clinical trial in ARG1-D subjects less than 2 years of age to assess safety and efficacy in order to provide support for the proposed inclusion of patients less than 2 years of age in the indication.

Product Quality

(b) (4)



(b) (4)



### Clinical Pharmacology

9. The adequacy of AEB1102 dosing in the context of initiating treatment via the subcutaneous (SC) route, without prior intravenous AEB1102 treatment, has not been characterized in patients with ARG1-D. Provide clinical data, either from an ongoing or planned trial, to support the dosing and safety (including immunogenicity) of initiating AEB1102 treatment via the SC route of administration.

### 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 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

**U.S. Food and Drug Administration**  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

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)

08/06/2025 07:08:09 AM