Mid-Cycle Meeting Summary

Application type and number: BL 125606/0
Product name: C1 Esterase Inhibitor Subcutaneous (Human)
Proposed Indication: For routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in adolescent and adult patients
Applicant: CSL Behring GmbH
Meeting date & time: December 12, 2016, 2:00 PM – 4:00 PM
Committee Chair: Felice D'Agnillo
RPM: Nannette Cagungun

Attendees:

Discipline	Name	Attended meeting?
Regulatory Project Manager (RPM)	Nannette Cagungun	Yes
Chair	Felice D'Agnillo, PhD	Yes
Clinical Reviewer	Laurence Landow, MD	Yes
CMC Reviewer	Matthew Williams, MSc Yiping Jia, PhD Tigist Kassa, PhD	Yes Yes Yes
Clinical Pharmacology Reviewer	Mahmood Iftekhar, PhD	
Pharmacology/Toxicology Reviewer	Jin Hyen Baek, PhD Mercedes Serabian Theresa Chen	Yes Yes Yes
OCBQ/DMPQ Reviewer	Donald Ertel	Yes
OCBQ/DMPQ/PRB Reviewer	Cheryl Hulme	No
Statistical Reviewer of clinical data	Lin Huo, PhD	No
Postmarketing Safety Epidemiological Reviewer	Jaspal Ahluwalia, MD	Yes
OCBQ/APLB Reviewer	Alpita Popat, PhD	Yes
OCBQ/BIMO Reviewer	Dennis Cato	Yes
OCBQ/DBSQC or OVRR/LIB Reviewer	Marie Anderson Hyesuk Kong, PhD	Yes Yes
Consult Reviewer(s)	NA	
OCBQ/DMPQ/Lead Inspector	NA	
CMC Inspector	NA	
Labeling Reviewer	NA	
Other Attendees	Renee Rees, PhD	Yes

Discipline	Name	Attended meeting?
	Michael Kennedy, PhD	Yes
	Deepa Arya, PhD	Yes
	Stephanie Simek, PhD	Yes
	Laurie Norwood	Yes
	Basil Golding, MD	Yes

Discussion Summary:

The review team has not identified any substantive issues or major deficiencies that would preclude approval of this BLA. However, further information/clarification will be requested to assist with the review of the application:

- CMC Information Request
  - Timeline for additional updated stability data
  - Information regarding process validation studies and (b) (4)
  - Sample request for (b) (4) vials of final product from each of the (b) (4) conformance lots (b) (4) .
- Update on clinical studies ongoing at time of BLA submission

1. Reviewer Reports.

   CMC-Product. Review of all assigned areas have been completed.

   - Drug substance and drug product process validation, comparability studies [Felice D'Agnillo].
   - Analytical Method Validation [Yiping Jia]
   - Reference Standards or Materials, Container Closure System, and Stability (b) (4) Drug Product [Matthew Williams]
   - Characterization of Drug Substance and Drug Product [Tigist Kassa]

   CMC-Product (DBSQC).

   - Quality Control [Hyesuk Kong]. Primary review will be completed by mid-January 2017.
   - Lot release protocol template and draft test plan [Marie Anderson]

   CMC-Facility/Equipment [Donald Ertel]. Primary review completion: January 27, 2017.

   Pharmacology/Toxicology [Jin Hyen Baek]. Primary review has been completed.

Clinical Pharmacology [Iftekhar Mahmood] Primary review will be completed by April 15, 2017

Clinical [Laurence Landow]. Primary review will be completed no later than February 1, 2017.

BioStatistics [Lin Huo]. Primary review will be completed by February 20, 2017.

Bioresearch Monitoring (BIMO) [Dennis Cato]. Primary review will be completed after receipt and review of the establishment inspection reports (EIRs).

Epidemiology [Jaspal Ahluwalia]. Primary review has been completed.

Advertising and Promotional Labeling [Alpita Popat]. Primary review will be completed by March 31, 2017.

2. For PDUFA V Program submissions, indicate whether discipline review letters will be issued.

   The review team does not intend to issue discipline review letters.

3. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation. N/A.

4. Determine whether Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.

   a. A Title IX PMR requiring SWG is not planned at this time.

   b. PMC: FDA acknowledges CSLB's commitment to completing their ongoing stability study.

5. National Drug Code (NDC) assignments to product/packaging (excludes devices).

   The NDC assignment for each product presentation is acceptable.

6. Proper naming convention.

   The review committee met and determined that the proper name for this product needs to include the route of administration to reduce the risk of medication errors. Inadvertent intravenous injection of the subcutaneous formulation could greatly increase the risk of the adverse reactions. ADRM has agreed. The review team determined that this product's proper name should be "C1 Esterase

Inhibitor Subcutaneous (Human)" to conform with CBER's proper naming convention.

7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).

    - Pre-license inspection of (b) (4) CSLB GmbH, Marburg facilities has been waived.

    - BIMO clinical investigator inspection assignments were issued for two domestic clinical investigators and one foreign clinical investigator conducting Study CSL830_3001. The inspections are pending, and are expected to be completed by the end of December, 2016. The BIMO reviewer will update the review committee as soon as the inspections have been completed and the EIRs received and reviewed.

Review:

8. Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g. Late-Cycle meeting, Advisory Committee, labeling discussion).

Mid-Cycle Communication	20-Dec-2016
Late-Cycle Meeting	13-Mar-2017
Labeling Target	31-May-2017
PMC Study Target	31-May-2017
First Action Due	30-Jun-2017
Proprietary Name Review	Acceptable 07-Sep-2016

9. Establish a labeling review plan and agree on future labeling meeting activities.

    Labeling meetings will be scheduled following completion of the clinical review.

Confirm, as applicable

10. Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.

    The Data Abstraction Team was notified of the CMC reviewer assignment on July 11, 2016.

11. New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry*. If not complete, indicate date it will be completed.

    This information has been entered in the database.

12. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

    Lot release will be by protocol review only. Lot release testing plan template was received from Marie Anderson on 11/28/16. Samples not officially requested.

13. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid *JA 900.01*: *Unique Ingredient Identifier (UNII) Code* for additional information.

    The UNII Code assignment request was sent to CBER SRS on August 18, 2016.

14. PeRC presentation date is set, and the clinical reviewer has addressed waiver/ deferral/assessment of the PREA decision.

    The applicant has requested a full waiver from pediatric studies because it has an orphan designation. This BLA does not have to be presented to PeRC.

15. **Action Items:**

    - The Mid-Cycle telecon is scheduled for December 20, 2016.
    - Additional information requests will be conveyed to CSL Behring within the next two weeks.

16. **For applications subject to the PDUFA V Program:**

    - The Late-Cycle Meeting is planned for March 13, 2017.
    - The Late-Cycle Meeting Materials will be sent at least 10 days before the Late-Cycle meeting.