

## Mid-Cycle Meeting Summary

**Application number:** BL 125668/o  
**Product name:** Immune Globulin Subcutaneous (Human)  
**Proposed Indication:** For treatment of primary immunodeficiency (PID) in adults  
**Applicant:** OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.  
**Meeting date & time:** Thursday, May 31, 2018, 1:30 PM-3:30 PM  
**Committee Chair:** Michael Kennedy, PhD  
**Meeting Recorder:** Edward Thompson

### Attendees:

Michael Kennedy	Wilson Bryan
Edward Thompson	Rachael Anatol
L. Ross Pierce	Kimberly Benton
Xiaofei Wang	Farshid Mahmood
Margaret Norton	Tejashri Purohit-Sheth
Nancy Eller	Lori Tull
Lu Deng	Laurie Norwood
Amanda Trayer	Robert McElwain
Randa Melhem	Dorothy Scott
Boris Zaslavsky	Shari Targum
Alpita Popat	Scott Proestel
Erin McDowell	Renee Rees
Hsiaoling (Charlene) Wang	Steve Winitsky
Leslyn Aaron	John Troiani
Varsha Garnepudi	Dennis Cato
	Suzanne Carter
	Maryna Eichelberger
	Lokesh Bhattacharyya

### Discussion Summary:

This meeting covered updates by the reviewers on the progress of the BLA review, and discussions of any pending actions that need to be completed by the action due date.

### Report and Discuss:

#### 1. Reviewer Reports.

DPPT CMC: No issues identified in the submitted reviewer report. Finishing up review of responses to IR. This task should be completed by August 24, 2018.

Clinical: Drs. Yeowon Kim and L. Ross Pierce have been conducting the clinical review. The following review tasks remain to be completed:

1. *Review of SAE narratives.*
2. *Review of four-month Safety Update, which is expected to be submitted 30 July 2018.*
3. *Comparison of outcome of secondary efficacy endpoints to those of other IGIV and IGSC product phase 3 trials.*
4. *Review of Protocol SCGAM-03 and non-IND Russian study SCGAM-04*
5. *Verification in conjunction with CBER statistician of applicant's table of adverse reactions.*

Dr. Pierce expects that the clinical review will be completed by October 29, 2018. No issues have been identified to date that could potentially impact approval unless the applicant does not agree to make requested changes to the draft package insert. There were no serious bacterial infections (SBIs) in the Phase 3 trial. The applicant will be asked to add the upper bound of the 99% confidence interval for the zero SBI rate to the draft PI to be consistent with other members of the class. It was noted that the Phase 3 clinical trial was conducted using an IGIV-to-IGSC dose conversion factor of 1.50, whereas the draft PI recommends using a value of (b) (4). It was further noted that the applicant recommends in the draft PI flexible dosing intervals ranging from daily to (b) (4). The applicant will be asked to change the draft PI to reflect how the product was administered in the Phase 3 study (weekly dosing using a dose conversion factor of 1.50).

It was noted that the BLA lacked separate analyses for the subgroup of subjects who completed all 12 months of the study. As agreed at the pre-BLA meeting, some pediatric subjects were ongoing as of the data cut-off date. Subgroup analyses for efficacy and safety were incomplete. Amendment 7 responded to FDA's March 14, 2018, clinical information request by providing data regarding serious and non-serious infections and adverse reactions for all subjects. These data were also presented as subgroup analyses by age and sex for the subset of subjects who completed the 12-month study.

While limited data from pediatric subjects have been included in the BLA, many of the pediatric subjects had not yet completed the Phase 3 study at the time of BLA submission, and it has not yet been determined whether there would be sufficient data from adolescents to allow the requested indication in adults to be extended to include adolescents. A pediatric assessment and recommendation will be presented to PerRC in this regard.

Clinical Pharmacology: No substantial issues identified. Pending IR (sent on 5/29/2018) response regarding bioanalytical method validation of clinical study pharmacokinetic samples. Review is ongoing.

Pharmacology/Toxicology: No issues identified in the submitted reviewer report.

DMPQ CMC Facility: Equipment cleaning and sterilization review is in progress, awaiting additional information to be submitted by applicant, in response to IR. Another IR will be sent after the MC meeting regarding the Qualification of Equipment, Container Closure, Aseptic Process Simulation, Sterile Filtration, and Shipping Validation.

Inspectional Status: The Pre-License Inspections for both the OPG Vienna Facility and the ODE Dessau Facility were waived. The concurred Inspection Waiver memos are in the EDR.

CMC reviewer (Analytical method and validation):  
Issues:

- Maltose (b) (4): validation issues for accuracy and LOQ
- Molecular size distribution ((b) (4)): validation issues for linearity and possible interactions between protein aggregates and (b) (4)
- Na+ (b) (4): SOP not adequately described; validation issues for linearity and LOQ
- Triton X-100 ((b) (4)): missing description for (b) (4) in SOP

Responses of pending IR (sent on 5/22/2018) are expected about 2 weeks. All SOPs and method validation issues are expected to be resolved through IR.

CMC review of Procoagulant Activity Assay: Review completed; IR pending for activity assay for linearity; August 10, 2018, is the date for final completion.

Statistical review: The clinical safety and clinical efficacy reviews are pending. There are no major issues at the time of mid-cycle. The primary efficacy endpoint was the overall clinical success in the rate of Serious Bacterial Infection(s) (SBI) (defined as bacteremia/sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia and visceral abscess) per person-year on treatment. There were no infections experienced during the course of this study meeting the criterion defined for SBIs. The applicant did not calculate the confidence limit for SBI using SAS software or any other method. I calculated the upper 99% confidence bound using StatXact 10. With zero SBIs in 54.77 person years of treatment with (b) (4) the study had a rate of 0.0 SBIs per subject per year (upper one-sided 99% confidence limit 0.08408), and therefore was successful in achieving the success criterion since the upper one-sided 99% confidence limit for the observed SBI rate per subject per year is <1.0. My estimate of the upper confidence limits for the number of other infections is different from the applicant's estimate which is not a substantive issue.

DBSQC Lot Release Protocol & Testing Plan: Review of the LRP template in progress; Product Testing Plan –draft testing plan in progress; Expected completion of review by August 8, 2018.

DBSQC CMC Bioburden: Review completed and uploaded to the EDR; Final Conclusion: After a thorough review of the information submitted in this BLA, this reviewer finds Octapharma (b) (4) drug product matrix is suitable for testing using their sterility, endotoxin, and diphtheria testing methods; these tests were qualified and performed in accordance with (b) (4), 21 CFR 640.104, respectively. In addition, the (b) (4) matrix is suitable for testing using their bioburden test method and the qualification was performed in accordance with (b) (4) >. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.

Pharmacovigilance plan (PVP): Review pending; Completion in September 2018.

Bioresearch Monitoring: BIMO inspections were issued for four sites conducting study SCGAM-01.

Site ID	Study Site	Location	483 Issued	Status
11	Faculty Hospital by St. Anna in Brno	Czech Republic	Yes	Inspection complete; pending receipt and review of EIR
42	University of California-Irvine	Irvine, California		Inspection pending
43	Toledo Institute of Clinical Research	Toledo, Ohio	Yes	Inspection complete; EIR review and classification in progress
47	Pediatric Pulmonary Associates of North Texas	Frisco, Texas	Yes	Inspection complete; pending receipt and review of EIR

Inspections have been completed for three of the four sites. The last site inspection is pending. When the inspections and EIR reviews are complete the committee will be updated with any significant findings.

Establishment Inspection Reports (EIRs) are pending receipt, review, and classification. Expected timeframe for receipt and review of EIRs is end of July 2018.

APLB: Advised on drafting and sending an information request for 10 suffix names.

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

No AC will be held for this application.

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

The timeline to draft potential Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) is for these tasks to be accomplished by November 29, 2018. A PREA PMC to submit a final study report for pediatric subjects in the ongoing Phase 3 trial is recommended.

4. National Drug Code (NDC) assignments to product/package (excludes devices).

Carton: NDC 68982 – 810 – 01

Container: NDC 68982 – 810 – 01

68982 assignment verified as Octapharma USA Inc with the (b) (4)

The RPM will draft an information request for new NDC numbers on the carton and container to comply with 21 CFR 207.35(b)(2)(ii)

5. Proper naming convention.

Immune Globulin Subcutaneous (Human) - acceptable

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

Reviewer Reports by DMPQ/CMC/Facility and BIMO provided this update as mentioned above.

## Review

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

Internal MC Meeting:	May 31, 2018
MC Communication Agenda to Applicant:	June 8, 2018
MC Communication with Sponsor:	June 11, 2018
Internal Late Cycle Meeting [LCM]	August 3, 2018
LCM Meeting Package Due to Applicant	August 24, 2018
External LCM with Applicant	September 6, 2018

Presented to review team with no comments in the meeting.

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

Labeling meeting to be scheduled in July 2018.

**Confirm, as applicable:**

9. 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.

CMC Reviewer noted no discrepancy.

10. New facility information is included in the application, requiring implementation of regulatory job aid [JA 910.01: Manufacturing Facility Data Entry](#). If not complete, indicate date it will be completed.

DMPQ CMC Reviewer: Information about OPG Vienna (Austria) and ODE Dessau (Germany) facilities is included in RMS-BLA.

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

Previously discussed in reviewer report.

12. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid [JA 900.01: Unique Ingredient Identifier \(UNII\) Code](#) for additional information.

UNII Code Assignment Request submitted on May 25, 2018.

13. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision. **Note:** Remind the Review Committee that PeRC forms need to be submitted two weeks in advance of scheduled PeRC meeting.

Discussed by clinical in item #1.

**Action Items:**

1. Draft and send MCC agenda to applicant.
2. Send IR for suffix names.
3. Send IR for revised NDC numbers on carton and container.

4. Schedule PeRC Meeting.
5. Schedule Label Meeting.

**For applications subject to the PDUFA/BsUFA Programs:**

1. Reach agreement on information to be included in the Mid-Cycle Communication telecon with the Applicant.
2. Reach agreement on dates for upcoming meetings such as the AC or Late -Cycle Meeting. **Note:** the RPM may choose to pre-populate these dates prior to the meeting.

See item #7 of the “Report and Discuss” section.