

Mid-cycle meeting summary

Application type and number: BL 125587/0

Product name: Immune Globulin (Human) 10%

Proposed Indication: Primary humoral immunodeficiency (PI); Chronic immune thrombocytopenia (ITP) in adults

Applicant: Octapharma Pharmazeutika Produktionsges.m.b.H.

Meeting date & time: September 29, 2015; 1130 – 1330

Committee Chair: Michael Kennedy

RPM: Christopher Hooban

Attendees:

Chairperson, CMC/Product	Michael Kennedy, PhD, OBRR/DHRR
CMC/Product	Lu Deng, PhD, OBRR/DHRR Malgorzata Norton, OBRR/DHRR Hsiaoling Wang, PhD, OCBQ/DBSQC Yonggang Wang, PhD, OBRR/DHRR Pei Zhang, MD, OBRR/DHRR
CMC/Other	Karen Campbell, OCBQ/DBSQC Simleen Kaur, OCBQ/DBSQC (submitted report but not present)
CMC/Facility, Equipment	Christian Lynch, OCBQ/DMPQ Randa Melhem, PhD, OCBQ/DMPQ
Pharmacology/Toxicology	Evi Struble, PhD, OBRR/DHRR
Clinical Pharmacology	Iftekhar Mahmood, PhD, OBRR/DHRR
Clinical	Laurence Landow, MD, OBRR/DHCR
BIMO	Erin McDowell, OCBQ/DIS Patricia Holobaugh, MS, OCBQ/DIS
Epidemiology	Wendy Paul, MD, OBE/DE
Statistical	Jiang Hu, PhD, OBE/DE
APLB	Alpita Popat, PharmD, MBA, OCBQ/DCM
RPM	Fatima Abbasi, OBRR Nannette Cagungun, MS, PD, RAC, OBRR Cherry Geronimo, OBRR Christopher Hooban, MS, MPH, OBRR
DH	Mahmood Farshid, PhD, Deputy Director, OBRR/DH Basil Golding, MD, Director, OBRR/DH
OBRR	Victor Baum, MD, OBRR/DHCR Dorothy Scott, MD, OBRR/DHRR Iliana Valencia, MS, OBRR/RPM
OCBQ	Qiao Bobo, OCBQ/DMPQ
OBE	Renee Rees, PhD, OBE/DB

Discussion Summary:

The Regulatory Project Manager, Christopher Hooban, began the meeting by presenting the agenda. This submission was received in CBER on April 15, 2015. The reviewers provided the status of their reviews.

Reviewer Report Discussions:

CMC/Process Development, Specifications, Control of Intermediates and Bulks, Raw Materials, Comparability of the Clinical Material, Conformance Lots (Malgorzata Norton)

All assigned areas have been completely reviewed. At this time there are no outstanding information requests. The following comments will be sent to the sponsor in the Lot Release Protocol IR:

1. Please state the (b) (4) titer specification as “(b) (4)”
2. Instead of “passed test”, please state the results of the (b) (4) Test.

The primary discipline review is scheduled to be completed by November 19, 2015. At this time no substantive issues have been identified.

CMC (Simleen Kaur*)

All assigned areas have been completely reviewed. There are no outstanding information requests. The primary discipline review is scheduled to be completed by October 1, 2015. At this time no substantive issues have been identified.

CMC (Hsiaoling Wang)

The “(b) (4)” method and validation review are completed. There are no outstanding information requests. The primary discipline review will be ready for laboratory chief review within two months. At this time no substantive issues have been identified. Surveillance testing was determined to not be needed at this time.

CMC/DBSQ Regulatory Coordinator (Karen Campbell)

The primary review has been completed. An IR for samples and comments on the LRP template will be sent to the applicant as an IR by October 1, 2015. The testing plan draft will be completed by October 1, 2015 and sent to the CMC reviewers for review. If there are no outstanding issues, the testing plan should be completed by February 12, 2016. Reagents for in-support testing will be requested once we are able to order the columns to perform the in-support testing. The columns are expected to be ordered by mid-October.

CMC/Process Validation (Yonggang Wang, Lu Deng, Malgorzata Norton)

To-date, all assigned areas have been completely reviewed. The primary discipline review will be completed by November 19, 2015. There are no outstanding information requests. The IR response was received a day before the internal midcycle meeting. A few issues have been

identified after initial review. Following a complete review of the response, additional issues may be identified and a second IR will be sent shortly thereafter.

CMC/Stability Section (Yonggang Wang)

To-date, all assigned areas have been completely reviewed. The primary discipline review will be completed by November 19, 2015. The reviewers indicated that there is not enough information on the consistency lot. There is one outstanding information request that was sent on September 24, 2015 with an expected response date of October 19, 2015.

A substantive issue was found in the application:

- The proposed storage condition is up to 24 months at 2-8°C. Within its shelf-life, the product may be stored at $\leq 25^{\circ}\text{C}$ for up to 6 months. The applicant provided the temperature excursion studies using both clinical lots and conformance lots in order to support this proposal. The study using clinical lots has been completed but the measles titers did not meet specification at the first month. The study using conformance lots are ongoing and the data will not be complete enough to support the current proposal.

This issue will not prevent approval of this BLA. The applicant can be informed that the proposed storage at $\leq 25^{\circ}\text{C}$ for up to 6 months within the shelf life will not be granted upon approval of this BLA, and the product shall be stored at 2-8°C during storage and transportation. The expiry labeling section should be changed accordingly.

CMC/Facilities (Christian Lynch, Randa Melhem)

Review of the original BLA submission regarding panzyga® manufacturing operations at the OSA Lingolsheim (France), OPG Vienna (Austria), and ODE Dessau (Germany) facilities is complete. A Pre-License Inspection (PLI) of the manufacturing operations at the OSA Lingolsheim facility is scheduled for October 5, 2015 to October 14, 2015 and will provide a better understanding of the manufacturing operations at this site. PLIs for the OPG Vienna and ODE Dessau facilities were waived as both facilities are licensed and the manufacturing operations for the product are similar to those of other US licensed products.

The initial BLA application lacked sufficient information for a thorough review. Three separate information requests were sent to the firm. Information requests received (amendment #'s 125587/0.9 and 125587/0.8) to date are currently under review. At this time there is one outstanding information request, which was sent on September 23, 2015, regarding the filling operations on Line (b) (4) and Line (b) (4) at the OPG Vienna facility and the visual inspection, packaging and labeling operations for the new presentations at the ODE Dessau facility.

The primary discipline review is scheduled to be completed by November 19, 2015. At this time there are no substantive issues that could have a potential impact on the review.

CMC/Virus Safety (Pei Zhang)

Review of the “Virus Validation Studies / Robustness Study Reports” has not been completed. The primary discipline review is scheduled to be completed by November 15, 2015. Key findings and substantive issues with the information and data in the application include:

- Robustness studies on the step of S/D treatment to include critical process parameters to demonstrate the effectiveness of S/D treatment step under the worst-case conditions of the manufacturing process.
 - o Plan for addressing: Robustness studies on the step of S/D treatment to include process parameters to demonstrate the effectiveness of S/D treatment step under the worst-case conditions.
- Tightening of the S/D (b) (4).
 - o Plan for addressing: Tightening of the S/D (b) (4) based on requested data.
- Set the specification for the column life-cycle and column cleaning validation study report.
 - o Plan for addressing: Set the specification for column life-cycle and column cleaning validation study report.

The reviewer has not identified any substantive issues that could lead to preventing approval.

Pharmacology/Toxicology (Evi Struble)

The following studies are still under review:

- Study (b) (4) 25046/1, Safety pharmacology/rabbits/Wessler
- Study (b) (4) 30210, GLP Safety pharmacology/rats/Wessler
- Study (b) (4) 30211, Local tolerance/rabbits
- Study (b) (4) 023613 Efficacy in mice

There are no outstanding information requests. The primary discipline review is scheduled to be completed by November 19, 2015. The reviewer has not identified any substantive issues that could lead to preventing approval.

Clinical Pharmacology (Iftekhar Mahmood)

To date, the pharmacokinetic study has not been reviewed. Re-analysis of PK data is needed (an information request will be sent to the applicant). The primary discipline review is scheduled to be completed by November 19, 2015. At this time the reviewer has not identified any substantive issues that could lead to preventing approval.

Clinical (Laurence Landow)

The following sections are still under review and are expected to be completed by October 3, 2015:

- Section 3.3 – Financial Disclosures

- Section 4 – Significant Efficacy/Safety Issues Related to Other Review Disciplines

There are no outstanding information requests. The primary discipline review is scheduled to be completed by October 15, 2015. Additionally, financial disclosure forms and review memos from other disciplines will be reviewed by this date. Key findings associated with each indication have been identified.

Regarding the primary humoral immunodeficiency indication, the primary endpoint (SBI rate per person-year <1.0) was met in pivotal study NGAM-01. One pediatric subject was discontinued from the study. No safety issues other than those previously reported with use of similar IgG products were noted in NGAM-01 or in extension study NGAM-05.

Regarding the chronic immune thrombocytopenia indication, the primary endpoint (increase in platelet count to $\geq 50 \times 10^9 / L$ within 7 days after the 1st infusion) was met in pivotal study NGAM-02, even though the study was terminated prematurely due to delayed availability of study medication after 40 of a planned 86 subjects had been enrolled. Secondary endpoint outcomes supported the primary endpoint outcome. Two subjects died, one from cerebral hematoma and the other from sepsis, both of which were product-unrelated. Of 8 non-fatal SAEs, all were product-unrelated except for a possibly-related aseptic meningitis SAE that ultimately resolved. No additional safety issues other than those previously reported with use of similar IgG products were noted in NGAM-02.

The available efficacy and safety data support approval for the PI and ITP indications from a clinical viewpoint.

BIMO (Erin McDowell)

Establishment inspection reports from three sites (Rush University, Seattle Children's, and University Hospital Brno) are still pending receipt and review. There are no outstanding information requests. The primary discipline review will be completed upon receipt and review of the outstanding three EIRs.

Inspections conducted for studies NGAM-01 and NGAM-05:

The inspection of Cardinal Glennon Medical Center (Site#02) was classified as VAI. Items on the FDA Form 483 included not increasing the subjects' dose when there was a 5% increase in body weight and two subjects with concomitant medications not reported. Other items discussed at the close of the inspection, included good documentation practices, medication lists being accurate, and appropriate adverse event reporting.

The inspection at Rush University Medical Center (Site#01) is pending completion.

The inspection at Seattle Children's Research Institute (Site#14) was split into 2 inspections. One for the original Clinical Investigator (CI) (483 issued; items included one informed consent form not including subjects complete name and two subjects receiving prohibited vaccinations during the study) and one of the CI who took over near the end of the clinical trial (district classified as NAI).

Inspections conducted for Study NGAM-02:

The inspection of Charite University Berlin Germany (Site#01) was classified as VAI. Items listed on FDA Form 483 included enrollment of an ineligible subject (#(b) (6)) due to age and platelet count and one subject dose calculation being incorrect.

The inspection of University Hospital Brno Czech Republic (Site#08) is pending completion.

At this time the reviewer has not identified any substantive issues that could lead to preventing approval.

Epidemiology/Pharmacovigilance Plan (Wendy Paul)

To-date, all assigned areas have been completely reviewed. There are no outstanding information requests. The primary discipline review is scheduled to be completed by October 5, 2015.

There were no thromboembolic events reported in any of the three clinical studies. There was one episode of clinically evident hemolysis in the NGAM-02 study, which is a labeled adverse event for human immunoglobulins related to its mechanism of action and removal of sensitized blood cells within the spleen. Hemolysis is also seen more frequently at the higher doses of IVIg (e.g. 1 g/Kg for two consecutive days) utilized in the treatment of ITP.

The risk management plan submitted with this application includes a pharmacovigilance plan outlining routine pharmacovigilance practices and labeling. Important identified risks include thromboembolic events (TEE), aseptic meningitis, hypersensitivity reactions, acute renal failure and hemolysis. Viral safety (i.e. viral transmission) is an important potential risk. There is missing information about safety in select patient populations including the elderly, pregnant or breast feeding women and patients with renal or hepatic impairment. The proposed risk management plan includes boxed warnings, written precautions and patient counseling information in the product label. At this time, routine pharmacovigilance is adequate to monitor the important identified and potential risks and missing information as described in the proposed pharmacovigilance plan.

At this time the reviewer has not identified any substantive issues that could lead to preventing approval.

Biostatistics (Jiang Hu)

The reviewer has not completed their review. Verification of some secondary efficacy endpoints in studies NGAM01 (for PID) and NGAM02 (for ITP) and verification of safety analysis for study NGAM02 need to be completed. There are no outstanding information requests. The primary discipline review is scheduled to be completed by October 15, 2015.

Key findings and substantive issues include:

- The primary efficacy endpoint of ngam-01, the SBI year rate, achieved 0.5033 as the upper one-sided 99% confidence limit and was less than the pre-specified reference value 1.0. Therefore the efficacy of PID treatment is supported. However, the 99% upper confidence limit of the adult group is higher than 1.0.
- The applicant submitted the interim data of ngam-02, which included only about 50% of the planned sample size. The response rate was observed as 29 of the 36 patients with the exact Clopper-Pearson 95% CI of 63.98% to 91.81%. The lower limit of the one-sided 97.5% confidence interval for the proportion of responders is above the pre-defined reference value of 0.6. Therefore the efficacy of the ITP treatment is supported.

At this time the reviewer has not identified any substantive issues that could lead to preventing approval.

Advertising and Promotional Labeling (Alpita Popat)

The proposed proprietary name was found acceptable. The labeling review is expected to be finalized by March 15, 2016. There are no issues that could prevent approval of this BLA.

The following information was also discussed:

1. Discipline review letters will not be issued at this time.
2. The application will not be discussed at an Advisory Committee.
3. The review team has not decided on whether Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REMS) is needed.
4. The National Drug Code is not uniquely assigned at each packaging level. The NDC numbers on the container and carton will need to be updated.

Size (ml)	Carton	Container
10	68982-820- 01	68982-820- 01
25	68982-820- 02	68982-820- 02
50	68982-820- 03	68982-820- 03
100	68982-820- 04	68982-820- 04
200	68982-820- 05	68982-820- 05
300	68982-820- 06	68982-820- 06

5. Components Information Table was obtained and notification to the Data Abstraction Team (DAT) made. CBER DCCABC was provided the names of the product reviewers on April 23, 2015.
6. New facility information is included in the application and has been entered in the database.
7. PeRC presentation is scheduled for January 13, 2016.
8. Proper naming convention. The recommended proper name is Immune Globulin Intravenous, Human 10%.
9. Unique ingredient identifier (UNII) code process has been initiated. A request for UNII Code was sent to CBER SRS on June 12, 2015.

Review

10. Major target and mile stone dates from RMS/BLA.

Application Received	4/15/15
Committee Assignment	4/18/15
First Committee Meeting	5/18/15
Filing meeting	5/28/15
Filing Action	6/4/15
Deficiencies Identified	6/4/15 (with Filing Letter)
Internal Mid-cycle Meeting	9/29/15
Mid-cycle Communication	10/20/15
Late cycle Meeting	1/07/16
Labeling Target Date	3/15/16
PMC Target Date	3/15/16
First Action Due	4/14/16
PNR	7/02/15 (Acceptable)
11. Initial labeling meeting has not been scheduled yet. It will be scheduled when the clinical reviewer has completed his review.

Action items:

1. The mid-cycle communication teleconference is scheduled for October 20, 2015, 1130 – 1230.
2. The RPM will send out an email regarding labeling review meetings by October 16, 2015.
3. Information Requests:
 - a. Iftekhar Mahmood intends to submit an information request to the RPM regarding the analysis of PK data.
 - b. Pei Zhang intends to submit an information request to the RPM regarding the following issues:
 - i. The concentrations of TNBP and TritonX-100 [(b) (4) Triton X-100 (b) (4) and (b) (4) TNBP (b) (4)] that are used for the viral inactivation by the S/D treatment are not the standard conditions ([(b) (4) Triton X-100 (b) (4) and (b) (4) TNBP (b) (4)]). Robustness study reports will be requested to ensure the effectiveness of viral inactivation at the TNBP concentration lower than (b) (4).
 - ii. (b) (4) range of the S/D (b) (4). The (b) (4) is (b) (4). Robustness study reports will be requested to ensure the effectiveness of viral inactivation at the worst-case conditions (for example less than (b) (4), less than (b) (4)).
 - iii. The step of Ion Exchange Chromatography is validated for viral reduction with two non-enveloped viruses (MEV and PPV). IR will be sent to clarify the specification for column life-cycle and column cleaning validation.

- iv. CMC/Process Validation reviewers will provide an IR to the RPM regarding the need for clarification to issues identified in the responses provided to previous information requests.
- c. The CMC/Process validation reviewers will provide a high level summary of their review and concerns to the PLI inspection team for discussion during the inspection.
- d. The statistical reviewer will provide the clinical reviewer an explanation as to why individuals were excluded from the NGAM02 (ITP) study.