

Mid-Cycle Meeting Summary, September 26, 2013 - Ruconest

Application type and number: BL 125495/0

Product name: C1 Esterase Inhibitor (Recombinant)

Proposed Indication: Treatment of acute attacks of hereditary angioedema (HAE) in adult and adolescent patients

Applicant: Pharming Group NV

Meeting date & time: September 26, 2013, 1:30 PM – 3:30 PM

Committee Chair: Elena Karnaukhova

RPM: Nannette Cagungun

Attendees:

Chairperson, CMC/Product	Elena Karnaukhova, PhD, OBRR/DH/LBVB
CMC/Product	Todd Mollan, JD, PhD, OBRR/DH/LBVB (Drug Product) Felice D'Agnillo, PhD, OBRR/DH/LBVB
CMC/Product	Dominador Manalo, PhD, OBRR/DH/LBVB (Drug Substance)
Animal Issues	John Dennis, DVM, MS, DAACLAM, OM/DVS
CMC/Facility, Equipment	Nancy Waites, MS, OCBQ/DMPQ/BI
Pharmacology/Toxicology	Jin Hyen Baek, PhD, OBRR/DH/LBVB Paul Buhler, PhD, OBRR/DH/LBVB
Clinical Pharmacology	Iftekhar Mahmood, PhD, OBRR/DH
Clinical	Charles Maplethorpe, MD, PhD, OBRR/DH/CRB
Statistical	Abigail Luo PhD, OBE/DB/TEB
BIMO	Anthony Hawkins, OCBQ/DIS/BMB
Epidemiology	Laura Polakowski, MD, OBE/DE/AEB
APLB	Alpita Popat, PharmD, MBA, OCBQ/DCM/APLB
DBSQC	Lokesh Bhattacharyya, PhD, OCBQ/DBSQC/LACBRP Hyesuk Kong, PhD, OCBQ/DBSQC/LMIVTS Catherine Poole, OCBQ/DBSQC/QAB
RPM	Nannette Cagungun, MS, PD, RAC, OBRR/DBA
DH	Basil Golding, MD, Director, OBRR/DH Paul Mintz, MD, Deputy Director, OBRR/DH Howard Chazin, MD, Deputy Director, OBRR/DH Mahmood Farshid, PhD, Deputy Director, OBRR/DH Nisha Jain, MD, OBRR/DH/CRB
OBRR	Betsy Jett, Deputy Associate Director for Regulatory

	Affairs, OBRR/IOD
DMPQ	John Eltermann, Director, OCBQ/DMPQ Laurie Norwood, Deputy Director, OCBQ/DMPQ
OBE	Manette Niu, MD, OBE/DE/AEB Boguang Zhen, PhD, OBE/DE/TEB Renee Rees, PhD, OBE/DB/TEB

Discussion Summary:

Nannette Cagungun, began the meeting by presenting the agenda and a brief overview of the regulatory history of this original BLA. This submission was received in CBER on April 16, 2013 and filed with deficiencies on June 14, 2013. It has an action due date of April 16, 2014. The Chair of the BLA, Dr. Elena Karnaukhova, described the product and its regulatory history from the time it was submitted as an IND to the time it was refused to file in February 2011.

The reviewers then proceeded to report the status of their review.

Discussion:

CMC (Elena Karnaukhova, Todd Mollan, Dominador Manalo)

Drug Product/Drug Substance:

The CMC reviewers have not identified any substantive issues to date. No CMC information requests (IR) are planned at this time but this could change as the review progresses. The CMC review will be completed by October 18, 2013.

Product Testing Plan: (Catherine Poole)

The draft testing plan was sent for initial review on September 3, 2013. In-support testing is in progress. There are no outstanding information requests.

Product testing: Microbiological Assay (Hyesuk Kong)

Bioburden review has been completed and the memo is under review. Review of the bacterial endotoxin test (BET) and the Sterility test will be completed after receipt of the applicant's response to the IR. Pharming Group NV committed to submit an additional qualification report to CBER by October 31, 2013. The drug product is currently tested for sterility at only the----(b)(4)---- facility. Pharming has committed to perform sterility validation at ----(b)(4)---- and provide information requested for the manufacturing site (---(b)(4)----).

There are no major substantive issues to resolve. The reviewer plans to complete the review by October 31, 2013.

Quality Control test Method and Validation (Lokesh Bhattacharyya)

The following analytical methods and their validations used for the lot release of the drug substance and the drug product were reviewed:

Drug Substance

----- (b)(4) -----
----- (b)(4) -----
----- (b)(4) -----

Drug Product

- 1. Potency by ----- (b)(4) -----
- 2. Purity and ----- (b)(4) -----
- 3. ----- (b)(4) -----
- 4. ----- (b)(4) -----

- 5. Water content by ---- (b)(4) ----
- 6. ----- (b)(4) -----
- 7. ----- (b)(4) -----

- 8. Assay for Host-(b)(4) Impurities of rh-C1NH by (b)(4)

The methods are appropriate and their validations are done adequately. A few deficiencies were identified in some of the test methods or their validation reports or both. An IR has been sent on September 17, 2013 to address these deficiencies and reviewers are waiting for the applicant’s response.

There is no substantive issue with the information and data in the application. However, additional information requests may be sent to the applicant after the response is reviewed. The review will be completed by November 20, 2013.

Laboratory Animal Medicine / Manufacturing (John Dennis)

There are no outstanding IRs or substantive issues. The manufacturing sections related to transgenic rabbit generation, care and maintenance are thorough and well-described. Internal procedures for daily checking of rabbit health, record-keeping, and follow-up decisions (other than euthanasia) and facility pest management -----
----- (b)(4) -----.

CVM has been invited to participate as a consultant on this review. The consult had only two questions: (1) Should the rabbits be screened for ----- (b)(4) -----, and (2) what is meant by the screening for “----- (b)(4) -----?” The answers to these questions do not have significant impact on the review.

The review will be completed by September 30, 2013.

CMC/Facility (Nancy Waites)

The review of the submission is ongoing. No information requests have been sent for drug substance or drug product review. An information request will be sent to answer

any issues as needed. There are no substantive issues identified for items that fall under DMPQ's purview at this time.

- Issues will also be covered during the pre-license inspections (PLI):
 - o Drug substance manufacturing facility

- ----(b)(4)----
 - -----(b)(4)-----
 - -----(b)(4)-----

o Drug product manufacturing facility

- ----(b)(4)----
 - -----(b)(4)-----
 - -----(b)(4)-----

o Rabbit production and milking facility

- -----(b)(4)-----
 - -----(b)(4)-----
 - -----(b)(4)-----

o Labeling and packaging facility

- -----(b)(4)-----
 - -----(b)(4)-----
 - -----(b)(4)-----

Drug Substance Review Issues

- Drug Substance --(b)(4)--
 - o More information is needed on the drug substance -----(b)(4)----- from the -----

------(b)(4)------(b)(4)-----

-----, --(b)(4)-- information will be reviewed ---(b)(5)--- and if issues arise they will be handled in future IRs.
- ---(b)(4)--- of ---(b)(4)--- milk

- The extent of clinical site monitoring during study 1310
- A request for recalculation of the primary endpoint for study 1310 after removing time-to-treatment outliers (this request is in response to the applicant's response to the File-with-Deficiencies letter)
- A request for more information on the Romanian HAE patient who died from laryngeal edema 25 days after completing the routine prophylaxis study 1207, and who is said not to have received a C1-INH containing product while hospitalized

The clinical reviewer identified the following substantive issues:

- There are no studies that justify the dose based on clinical outcomes.
 - o The dose was chosen based on theoretical considerations about plasma C1-INH activity levels.
 - o FDA advised the sponsor to find the minimum effective dose through dose exploration studies, but this advice was not followed.
- Pivotal study 1310 has met its primary endpoint.
 - o However, efficacy has not been demonstrated in the following prespecified subgroups:
 - U.S. subjects (half of enrollment)
 - Female subjects (63% of enrollment)
 - o This was noted in the June 14, 2013, File-with-Deficiencies letter, and the applicant has given an inadequate explanation for this in a July 26, 2013, response letter.
- Analysis of the database structure for study 1310 supports the conclusion that the U.S. and European study sites were not conducted in a similar manner.
 - o Therefore, I conclude that data from these two geographical sites cannot be combined.
- Efficacy results not consistent across studies 1205 [100 units or 50 units or placebo], 1304 [100 units or placebo], and 1310 [50 units or placebo].

The lack of consistent results across studies 1205, 1304, and 1310 do not permit a recommendation for licensure at this time. An additional efficacy study that has a dose-comparison design and that is conducted within the U.S. with gender-balanced enrollment should be performed. A clinical dose-effect should be demonstrated in this study.

Dr. Maplethorpe will complete his review of the application by December 1, 2013.

BIMO (Anthony Hawkins)

The following BIMO areas not completely reviewed to date:

Receipt and review of five completed BIMO inspection reports involving both foreign and U.S Protocol C1 1310 clinical study sites *

- * Skopje, Macedonia (7 subjects) - pending completion of BIMO inspection
- * Târgu-Mure, România (9 subjects) - pending completion of BIMO inspection
- * Krakow, Poland (7 subjects) - pending completion of BIMO inspection
- * Lake Oswego, Oregon (25 subjects) - pending completion of BIMO inspection
- * Atlanta, Georgia (17 subjects) - pending completion of BIMO inspection

The BIMO-requested completion date for the above inspections is September 17, 2013.

There are no outstanding BIMO information requests. The target timeframe for BIMO review of the above pending inspections is 30 days after CBER receipt of each inspection report

No substantive BIMO findings or substantive issues have been noted at this time.

The review committee will be informed about the results from the above BIMO inspections as soon as the information becomes available.

Epidemiology (Laura Polakowski)

The review has been completed, with the exception of more expansive review of supporting materials. There are no current outstanding Information Requests. An additional IR will be submitted to inquire about the following:

- An additional IR will be submitted to inquire about the following:
 - AE Case Report for Site/Patient # 071/(b)(6) (Study 1304) & 204/(b)(6) (Study 1310)
 - 57 yr old Male who experienced a myocardial infarction 73 days after 1st dose of rhC1INH in 1304 OLE; AE was considered by the investigator to be “definitely not related” to the study treatment.
- FDA will inquire about the determination of relatedness of the AE to the study drug and why this determination was made as well as request any additional information regarding risk factors for cardiovascular disease or thrombosis in this patient.
 - Sequence 0003, Section 1.16 (Risk Management Plan), dated May 23, 2013
 - P.32, Populations Not Studied in the Pre-licensure Phase, Pediatric Patients: This section mentions a Pediatric Investigation Plan for the EU that involves a study that will evaluate the safety, immunogenicity, pharmacokinetics and efficacy of rhC1INH for the treatment of acute HAE attacks among patients 2-13 years of age (Study 1209).
- FDA will request a summary of the protocol for this study.
 - P. 53, Signal Detection
- FDA Question: For additional clinical trials data, what specific methods will be used to assess:
 - Whether the frequency or severity of an AE is significantly greater among those receiving rhC1INH vs. placebo?

- Whether the temporal relationship between an exposure and an AE is significantly greater among those receiving rhC1INH vs. placebo?
- Whether the frequency of an AE is increasing at a significantly greater degree with increasing dose of rhC1INH vs. placebo?
- FDA Question: What specific methods will be used in performing signal detection analyses among post-marketing HAE Registry data?
- FDA Question: What specific methods will be used in performing benefit-risk analyses among post-marketing data?
 - P.56, US HAE Registry
- FDA Question: Is this a new registry that will also include pdC1INH products already approved in the US?
- FDA Question: What specific information will be collected on each patient receiving rhC1INH treatment? (i.e., is there a protocol or protocol summary FDA can review for this registry?)
 - P.58, Table 24. Adverse Event Data Capture Aid Summary: This table lists the relevant MedDRA or Non-MedDRA verbatim terms that will be used to identify AEs using the Data Capture Aids; FDA notes that the Preferred Terms (PTs) for TEEs (i.e., infarction, ischemia) are likely not specific enough to capture all potential AEs of interest (i.e., myocardial infarction, cerebral ischemia) and some PTs for hypersensitivity reactions (e.g., Type I hypersensitivity reaction) may be too specific to capture all potential allergic AEs of concern that may be reported by a patient or provider as a sign, symptom, or less specific term (e.g., anaphylaxis, shock, respiratory distress or difficulty breathing, angioedema, inspiratory stridor, bilateral wheezing, urticaria, serum sickness, delayed hypersensitivity reactions).
- FDA Recommendation: Please provide FDA with a more comprehensive list of MedDRA PTs that will ensure adequate capture of the following potential AEs of concern: allergic reactions, including anaphylaxis, shock, respiratory distress or difficulty breathing, angioedema, inspiratory stridor, bilateral wheezing, urticaria, serum sickness, and delayed hypersensitivity reactions, and all reports of thrombosis, including deep venous thrombosis, pulmonary embolism, ischemic colitis, myocardial infarction, stroke, transient ischemic attack, and cerebrovascular accidents (excluding device-related thrombosis).
 - P.59, Data to be Collected (using the Data Capture Aids)
- FDA Question: How complete and how timely will data collection be? Will multiple queries occur until all information about an AE is obtained for its specific category? What ensures adequate and timely follow-up of any incomplete information?

The reviewer indicated that the primary discipline review will be completed pending additional information from new IR, as well as review of expanded review of supporting documents, as noted above: (September 18, 2013)

The issues have no impact on approval although the applicant will need to provide additional information regarding Signal Detection and Benefit-Risk Methods. Identified issues would need to be followed post-approval using pharmacovigilance methods described in the Risk Management Plan.

Biostatistics (Abigail Luo)

The review will be completed by December 1, 2013. There are no outstanding information requests at this point. However, information request is planned (See points d and e below.). The following items describe the key findings and substantive issues with the application:

- Study 1205 (started out as a Phase 2 trial) and 1304 (100IU/kg dose) are of limited values for assessing efficacy, because of their less rigorous design and conduct, compared with study 1310. For example, the assessment of the primary endpoint, time to beginning of relief of symptoms based on VAS, was less frequent and of shorter duration, i.e., at 15m, 30m, 1h, 2h, 4h, and if still hospitalized, at 8h and 12.
- The applicant's explanation for the lack of efficacy in female subjects of the primary endpoint based on TEQ in the confirmatory study 1310, in series 5 (July 29, 2013) in response to FDA's June 14, 2013 filing/deficiency letter, is inadequate.
 - The applicant believed that efficacy was not demonstrated for the female subjects because there is a delay for presentation for evaluation from onset of angioedema attack in the placebo arm in females compared to the males (268 minutes versus 186 minutes, see Table 1). However, the delay presentation in females may be partially accounted for by "outliers" (at least two cases, 1090m and 955m in the females, Table 2). Thus more analysis should be performed taking into account the "outliers", and more forms of analysis may be needed to understand the contribution of "time from onset of attack to evaluation" to the efficacy assessment.
 - Even if "time from onset of attack to evaluation" is statistically significant in models involving the primary endpoint, whether it is the main driver in not being able to demonstrate efficacy in females will entail clinical judgment.
 - As stated under item 2.a above, there are at least two "outliers" in the female subjects in regards to time between attack onset and evaluation, i.e., 1090m (18.2h) and 955m (15.9h). One of the inclusion criteria for eligible attack is that the evaluation should occur within 5 hours of attack onset. Information request regarding these two subjects may need to be sent.
- There is a confounding of gender effect (female, male) with region effect (US, Rest of the World (ROW)). The assignment of patients to treatment arms were centrally randomized, stratified by gender (female, male) and primary attack location (abdominal, peripheral, facial, oropharyngeal-laryngeal (OPL)). See Table 3 for details. For example, the USA placebo group female to male ratio is 7:1 and the ROW placebo group female to male ratio is 1:2. This ratio is 1:1 for the USA rhC1INH group and 3.4:1 for the ROW rhC1INH group. Therefore, any assessment of reasons not able to demonstrate efficacy in the females may not be done independent of the assessment of not able to demonstrate efficacy in the US.
- There is substantial censoring in the Saline arm; 13 of the 31 (42%) of subjects randomized to the Saline arm received rescue medication, i.e., rC1INH. It appears that some of these subjects received the rescue medication prior to the 4h assessment, which is the time point the protocol says rescue medication should be considered if symptom relief has not begun by that time. We will assess the implication of this observation after looking into the reasons that rescue medications were given for each of the subjects receiving the rescue medication.

There may be difficulty in interpreting the efficacy results in the females and the US if no satisfactory reason can be found to explain why efficacy was not demonstrated in these two groups.

Advertising and Promotional Labeling (Alpita Popat)

The proposed proprietary name was found acceptable. The labeling review is expected to be finalized by November 15, 2013. There are no issues that could prevent approval of this BLA.

Nannette Cagungun provided the following information:

1. Discipline Review Letters will not be issued at this time.
 2. Clinical review findings will be potential issues for presentation to the Advisory Committee if a decision is reached to hold BPAC.
 3. The review team has not decided whether Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REMS) is needed.
 4. The National Drug Code (NDC) is not uniquely assigned at each packaging level. Pharming will be asked to correct the NDC numbers on the container and carton labels.
 5. Proper naming convention. The recommended proper name is C1 Esterase Inhibitor (Recombinant).
 6. Components Information Table was obtained and notification to the Data Abstraction Team (DAT) made. The CMC reviewers have been given access to the database.
 7. New facility information is included in the application and has been entered in the database.
 8. In-Support Testing is being performed. This was decided through the May 9, 2013 testing meeting. If this product is Exempt, the Lot Release Protocol is not applicable. If it is not going to be Exempt, a Lot Release Protocol Template will need to be requested and reviewed.
- **Post-licensure CBER confirmatory lot release testing-** If the product is not going to be Exempt, this will need to be decided so that it can be documented in the testing plan.
 - **Product Testing Plan** – The Draft Testing Plan was sent (via email) for review on September 3, 2013 with responses/edits requested by COB on October 4, 2013.
9. Unique ingredient identifier (UNII) code process has been initiated. A request for a UNII Code was sent to CBER SRS on July 5, 2013.
 10. This product has an orphan designation and does not require PeRC presentation.
 11. The review team will meet again to reach agreement on information to be included in the Mid-cycle communication with the applicant.

Review

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

Application Received 4/16/13
Committee Assignment 4/16/13
First Committee Meeting 5/8/2013
Filing meeting 5/31/13
Filing Action 6/14/13
Deficiencies Identified 6/14/13 (with Filing Letter)
Internal Mid-cycle Meeting 9/26/13
Mid-cycle Communication 10/10/13
Late cycle Meeting 1/16
Briefing Package 1/3/14
Labeling Target Date 3/17/14
PMC Target Date 3/17/14
First Action Due 4/16/14
PNR 7/28/13 (Acceptable)

13. Pending dates of targets and milestones (e.g. late-cycle meeting, Advisory Committee, labeling discussion).

- The late-cycle meeting has been scheduled for Thursday, January 16, 2014 at 2:30 pm.
- The decision to present this BLA to the Blood Products Advisory Committee has not been made as of yet.

14. Initial labeling meeting is scheduled for October 29, 2013 at 10:30 am.

Action items:

- The mid-cycle communication teleconference is scheduled for October 10, 2013 at 11:30 am.
- An internal meeting will be scheduled to discuss clinical/statistical issues prior to October 10, 2013.