
Report of Telephone Conversation

Submission Type: BLA **Submission ID:** IND 15089 **Office:** OBRR

Title/Product:

Coagulation Factor Xa (Recombinant), Inactivated [ANDEXXA]

Applicant: Portola Pharmaceuticals Inc.

Telecon Date/Time: March 14, 2016 4 p.m. – 5 p.m. **FDA Initiated:** No

Communication Category/Subject:

OTHER - To discuss Portola's concerns regarding the meeting summary issued on March 7, 2016 (reference CRMTS 10105).

Telephone Number:

1-877-668-4490 Call-in toll-free number (US/Canada)

(b) (4) Attendee access code

FDA Participants:

Bindu George, MD – Branch Chief, OBRR/DHCR/CRB

Christopher Jankosky, MD – Director, OBE/DE

Howard Chazin, MD, MBA, Acting Director, OBRR/DHCR

Jay Epstein, MD, Director, OBRR

Renee Rees, PhD – Stat Team Lead, OBE/DB/TEB

Thomas J. Maruna, MSc, MLS(ASCP), CPH, Regulatory Management, OBRR

Portola Participants:

John Curnutte

Janice Castillo

Alex Gold

Bill Lis

Teleconference Discussion:

This teleconference was requested by Portola in response to the meeting summary issued on March 7, 2016 under IND 15089 for the type-A meeting CRMTS 10105. Portola stated that they do not agree with FDA's meeting summary regarding the ANNEXA-4 prospective control cohort citing CBER's request to define a superiority endpoint for the prospective cohort and include a statistical test against standard or usual care treatment as their principal concern.

Portola contended that during the meeting they agreed to enroll a prospective control cohort, as a compromise, if it is designed as an observational cohort and that CBER consider the study to be

“exploratory” to first determine if interpretable data can be obtained. Portola stated that the requirements for the prospective control cohort stated in the FDA’s March 7, 2016 [CRMTS 10105] meeting summary, as described above, do not reflect this; that such agreements were not made and are unacceptable to Portola.

Portola maintained its past position that a prospective cohort would be too confounding and the data therefore uninterpretable. Portola stated that it does not believe a detailed statistical analysis plan was agreed upon or would be consistent with a “feasibility” study.

FDA maintained its position and reiterated that the Agency repeated several times in the meeting that the prospective cohort study should be designed to serve as the control arm of the Phase 3b/4 study and have a superiority endpoint. FDA reminded Portola that is why an interim analysis, including a sample size re-estimation, was recommended in addition a revised Statistical Analysis Plan (SAP). Further, FDA noted that in some cases when a superiority trial does not win on superiority, the Agency may allow some degree of flexibility in accepting the submission (prior approval efficacy supplement) for review based on the totality of data provided the effect size was favorable to ADNEXXA, taking into consideration the risk-benefit profile of ADNEXXA and supportive data from the (b) (4) study.

FDA reiterated that the totality of the data will be taken into consideration and would include:

- The results of the ongoing bleeding study, ANNEXA-4
- The proposed (b) (4)
- The PK/PD data including the (b) (4)

FDA noted that the bulk of data would be submitted postmarketing and that Portola and the Agency would have to agree upon what that would include.

With respect to the prospective cohort study, FDA directly stated that it could not accept the study design without a SAP. FDA again proposed an interim analysis, to determine feasibility, whereby the protocol could be modified in real-time, but it must be designed as a superiority study. FDA reiterated its request for a protocol design and acknowledged future negotiation and revision would be inevitable. Further, FDA noted that even in the event of failure to demonstrate superiority, the Agency would consider the totality of the data as noted above.

With respect to the design, FDA informed Portola that stratification, across inhibitors, is not necessary if Portola is confident that the drug effect is the same across all inhibitors, but that Portola was accepting a risk, particularly if the drug effect is not the same across all inhibitors.

Portola agreed to provide a protocol synopsis by March 21, 2016, but stated that if it was not accepted that the applicant would escalate the issue through CBER management (i.e. beyond OBRR). FDA agreed to accept a synopsis by March 21, 2016 provided that Portola submit a full protocol, including a SAP, by April 15, 2016; FDA agreed to provide statistical feedback after

review of the synopsis. Portola agreed to provide a “high-level” SAP. Portola also stated that it plans to submit a synopsis for the (b) (4) and include stopping rules for interim analysis. FDA informed Portola that the (b) (4) study should be submitted to the IND for review, but was not expected to be reviewed during the current BLA review cycle.

Note:

Portola was asked to submit its formal dispute of the meeting summary [CRMTS 10105] as an amendment to IND 15089 via email on March 9, 2016 from the Regulatory Management Officer, Thomas J. Maruna. Portola is yet to submit its formal dispute.

Portola was asked by the Director, OBRR to submit its version of the meeting minutes for February 24, 2016 [CRMTS 10105]. Portola is yet to submit its version of the meeting minutes.

END