

MEETING MINUTES

TELECONFERENCE WITH BLA 125586 PORTOLA PHARMACEUTICALS INC.

MARCH 23, 2018

PORTOLA ATTENDEES:

Michele D. Bronson, PhD, Vice President, Development Operations
Janice Castillo, Senior Vice President, Regulatory Affairs
Pamela Conley, PhD, Senior Vice President, Biology and Pharmacology
John Curnutte, MD, PhD, Executive Vice President, Research and Development
Jack Lawrence, MD, Senior Vice President, Chief Medical Officer
William Lis, Chief Executive Officer
John B. Moriarty, JD, Executive Vice President and General Counsel
Evangelia Raptis-Zarou, MS, Director, Regulatory Affairs
Dana Redhair, Senior Director, Regulatory Affairs
Sonia Souza, PhD, Senior Director, Biometrics
Patrick Yue, MD, Senior Director, Clinical Development

Advisors:

Stuart J. Connolly, MD, FRCPC, Professor, McMaster University, PI, ANNEXA-4 Study

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FDA ATTENDEES:

Faith Barash, PhD, CBER/OBE/DE (Pharmacovigilance)
Kimberly Benton, PhD, CBER/OTAT (Deputy Director, OTAT)
Chunrong Cheng, PhD, CBER/OBE (Biostats)
Bindu George, MD, CBER/OTAT/DCEPT (Clinical)
Ilan Irony, MD, CBER/OTAT/DCEPT (Deputy Director DCEPT)
Adamma Mba-Jonas, PhD, CBER/OBE/DE (Branch Chief)
Celene Moorer, CBER/OTAT/DRPM (RPM)
Mikhail Ovanesov, PhD, CBER/OTAT/DPPT (CMC)
Scott Proestel, PhD, CBER/OBE/DE (OBE Reviewer)
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT (Director, DCEPT)
Ramani Sista, PhD, CBER/OTAT/DRPM (Director, DRPM)

Boguang Zhen, PhD, CBER/OBE (Director OBE)

Discussion:

Portola Pharmaceuticals provided FDA with a PowerPoint presentation submitted on March 22, 2018.

Referring to the PowerPoint presentation discussed the agenda and their reaffirmation of Accelerated Approval status for ANDEXXA. Portola inquired if this study would be a post marketing requirement. FDA stated that the BLA was still under review and could not comment.

Preliminary Discussion of RCT:

Portola discussed the following issues related to comments sent to Portola on March 22, 2018.

A2: Concomitant use of coagulation factors and andexanet: Portola stated that they did not want sites to use coagulation factors in ANDEXXA due to safety concerns. The FDA stated that if the protocol specified that subjects in the ANDEXAA arm could not receive concomitant therapy with coagulation factors, the plan would be acceptable. Nevertheless, the Applicant would need to specify a plan for adjudicating outcomes if subjects in the ANDEXXA arm were to receive coagulation factors concomitant or within the efficacy observation period.

B: Exclusion of patients taking edoxaban from the FDA's RCT study comments: Portola questioned if this was a safety or efficacy concern. Portola stated that they would like to include the edoxaban group due to worldwide use. FDA stated it was Portola's choice. FDA noted that the intent of the PMR study would be to evaluate for efficacy in subjects receiving ANDEXXA for reversal of apixaban and rivaroxaban related bleeding, the FDA's primary interest would be the efficacy in this population. Therefore, the FDA requested that Portola provide a hierarchical analysis plan that was based on evaluating efficacy as in primary efficacy analysis in the population who required ANDEXXA for the reversal of apixaban and rivaroxaban related bleeding first followed by an efficacy analysis in all subjects.

C1: Antibody evaluation after Day 37 from the FDA's RCT study comments: Portola asked for clarification regarding the antibody testing after Day 37. FDA stated there was not a clear understanding as to how long these antibodies persisted. Portola insisted that the antibodies did not persist and is unsure why they would need to be tracked. FDA stated that in the ANNEXA 4 study, anti-ANDEXXA antibodies were observed at the time of last follow up for subjects. Therefore, FDA requested that Portola continue follow up for anti-ANDEXXA antibodies. Portola inquired whether longer follow up (than the proposed follow up) could be limited to patients with anti-ANDEXXA antibodies that persisted until Day 30 follow-up. FDA stated that the plan was acceptable.

G1 i-iv: Adjudication criteria for discrepant findings, from the FDA's RCT study comments: FDA requested that Portola provide additional clarity and additional justification from Portola.

F4: Sample size and hypothesis testing, from the FDA's RCT study comments: FDA stated that Portola needs to modify the sample size justification to be consistent with the hypotheses. The magnitude of benefit is a review issue.

In conclusion, the FDA requested Portola to submit the revised protocol as soon as possible along with the SAP. Portola agreed.