BLA 125586 Supplement 0, Response to Complete Response Letter

Applicant: Portola Pharmaceuticals

Receipt Date: August 4, 2017

Action Due Date: May 4, 2018

Review Type: Addendum to Clinical Review Memo to provide status of the Post-Marketing Required Study (PMR Study)

Clinical Reviewer: Bindu George, M.D.

Date Completed: May 2, 2018

Supervisory Concurrence: Tejashri Purohit-Sheth, M.D. (Director, Division of Clinical Evaluation and Pharmacology Toxicology)

The purpose of this addendum is to provide an update regarding the status of the Post Marketing Required (PMR) Studies under Accelerated Approval and clarify information provided in the clinical review memo dated April 23, 2018 to reconcile the information provided in Sections 5.2 and 6.1 of the label.

The PMR study was submitted for review as a first draft under BLA 125586 and submitted on March 16, 2018. Subsequent versions were submitted under IND 15089 as Amendments 216, submitted on March 30, 2018 and Amendment 219, submitted on April 17, 2018.

Post Marketing Required Study

The sponsor will conduct Study -18-513, titled "A Phase 4 randomized trial of ANDEXXA in acute intracranial hemorrhage in patients receiving oral factor Xa inhibitors" in 440 subjects randomized in a 1:1 manner.

Adult subjects with acute intracranial hemorrhage are eligible if the ICH is radiographically confirmed within 2 hours prior to randomization. Subjects should have received rivaroxaban, apixaban or edoxaban within 15 hours of randomization. Subjects will be randomized to low-dose or high-dose ANDEXXA depending on the time from last dose of any of the three anticoagulants or usual care (physician's choice) other than ANDEXXA. Four hundred and forty subjects will be enrolled and randomized in a 1:1 manner to ANDEXXA or usual care (any treatment at physician's discretion) with the exception of ANDEXXA. The efficacy-evaluable population will consist of all randomized subjects. Hemostatic outcomes will be assessed clinically by National Institute of Health Stroke Scale (NIHSS) and by radiographic imaging (CT or MRI) at 12-hours post-randomization for primary efficacy analysis. The safety observation period for immediate adverse events will be for 3 days and delayed adverse events will be weekly until 30 days post-treatment with ANDEXXA. A separate PMR study for safety is not recommended at this time, as data from 220 subjects (who receive ANDEXXA) may be sufficient to evaluate the safety of the study. The study is an open-label study with efficacy

assessments performed by a blinded endpoint adjudication committee. Sample size calculations were performed based on the assumption that a total sample size of 400 subjects will provide a 90% power to detect at 0.05 two-sided significance level, a difference in hemostatic efficacy of 65% for the usual care arm and 80% for the treatment arm. An interim analysis is planned when 50% of the sample size has completed adjudication for efficacy and study stopping is planned for efficacy.

The following milestones are provided, of which the milestones in bold text are required milestones per the PMR requirements:

- **Submission of the Study Protocol: April 17, 2018** (submission date to IND 15089)
- First patient enrolled: January 31, 2019
- **Completion Date of Patient Accrual: September 30, 2022**
- Study Completion Date: October 31, 2022
- **Date of Final Study Report Submission: April 2023**

Reviewer comments: Issues identified during the review of the first and second versions of the protocol for Study 18-513 were related to the study design, treatment plan with concomitant medications bleeding, adjudication and assessment of safety. These issues were resolved through two interactions with the Applicant; a teleconference held on March 23, 2018 following which Amendment 216 was submitted on March 30, 2018 and an IR request sent on April 13, 2018 following which the Applicant submitted a revised protocol under Amendment 219 on April 17, 2018. The revised study submitted under Amendment 219 of the IND was found to be acceptable. The safety monitoring plan was reviewed by the epidemiological review team in the Office of Biostatistics Evaluation and recommendations to enhance post-marketing safety is being deferred to the review team. The statistical analysis plan was reviewed by the statistical review team. The protocol submitted under Amendment 219 is found acceptable to meet the stated objectives. The Applicant submitted the PMR study (the identical study in Amendment 219) under the BLA on April 26, 2018. This PMR study is found acceptable and an IR request was sent on May 1, 2018 to revise the milestone dates to reflect the date of submission of the RCT study protocol to the IND.

The Usual Care Cohort Study and the ANNEXA 4 study are not considered PMR or Post-Marketing Commitment (PMC) studies.

Clarification for Section 5.2 of the label

The label notes that 11 patients who were anticoagulated with rivaroxaban had baseline anti-fXa activity levels > 300 ng/mL. Table 10 of the clinical review memo dated April 23, 2018 did not include analyses as conveyed in the label, but aggregated data for subjects treated with apixaban and rivaroxaban. The reviewer confirms the analyses as noted in Section 5.2 of the label. The reviewer notes that 10 subjects had screening levels >300ng/mL and 1 subject (Subject (b) (6) did not have screening levels available, but level drawn at study drug administration were >300 ng/mL. Therefore, for analysis purpose, this subject is noted to have baseline level > 300ng/mL.

Clarification for Section 6.1 of the label

Table 5 of the reviewer's memo dated April 23, 2018 includes analyses of the deaths by bleeding type based on the percentage of subjects with bleed type who died. For example, the review memo of April 23, 2018 notes, of the 25 subjects who died, 15 ((60%) subjects entered the study for ICH related bleeding. Section 6.1 of the label includes an analysis of the percent of subjects with a bleed type that died. For example, the label notes, of the 106 subjects with ICH in the study, 15 (14%) died. The reviewer confirms the analyses provided in Section 6.1 of the label.