Addendum to Clinical Review Memorandum BLA 125506.46

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Clinical Review

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In the Clinical Review of BLA 125506.46 (September 18, 2018) it was recommended that the existing PMC to study major surgery in patients with moderate and severe factor X deficiency be limited to study of major surgery in patients with severe factor X deficiency, concomitant with approval of the indication for perioperative management of surgery in patients with moderate and severe factor X deficiency.

The Sponsor (BPL) was invited to submit a new PMC, based on the existing PMC, but limited to study of major surgery in severe factor X deficiency, and was offered the opportunity to delay the milestones for protocol submission, study completion, and submission of study report to the FDA.

During a teleconference with the Sponsor (BPL) conducted September 19, 2018, BPL stated that it would be logistically easier for them to keep the current PMC as written, since multiple IRBs would have to be asked to accept amendments to existing protocol Ten06. They also wish to adhere to the original milestones because they think they will very shortly have three major surgery cases to present, two of which are severe, and one of which is moderate. The FDA clinical review team believes that in light of the rarity of the disease and low frequency of surgical procedures in this population, particularly major surgery, that submission of three cases, to include two severe factor X deficiency patients will suffice to fulfill the PMC if they are well-characterized with factor X levels achieved at the time of surgery. The moderate case to be included would improve our confidence in surgery in moderate factor X deficiency, and would be welcome, though not required. During the teleconference we offered them the option of including data on factor X peak levels achieved with COAGADEX associated with treatment of severe bleeding episodes on-demand, to support efficacy of COAGADEX for surgical procedures.

Please note, all of this is retrospective data that is being obtained from hemophilia treatment centers that have already done the procedures (data mining). Inclusion of additional patient data does not pose additional risk to human subjects.

For these reasons, the Sponsor's proposal to continue under the terms of the existing PMC is satisfactory and should be accepted.