FDA Consultation: Andexanet (Part 2)
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6. In healthy subjects who received rivaroxaban, apixaban and edoxaban, andexanet caused a transient but significant decline in anti-FXa activity during and shortly following a 2 hour infusion. This was followed by a return of anti-FXa levels to approximately 50% of initial levels with a subsequent decline as expected based upon the individual anticoagulant's half-life. For each of the aforementioned anticoagulants, please comment on:

a) The adequacy of the depth of reversal, as evidenced by reduction in anti-FXa activity and unbound anticoagulant. Specifically, please comment on the clinical significance, if any, of the nadir levels of anti-FXa activity for each of the three anticoagulants that are observed after the administration of andexanet. Do these levels predispose actively bleeding subjects to risk of continued bleeding? Is there an acceptable (target) level of anti-FXa activity that correlates with a reduced risk of bleeding? Is the target 30 ng/ml proposed by the applicant an acceptable target level for each of the anticoagulants? If not, what data would be necessary to identify an appropriate therapeutic target level, below which reduction in anti-FXa activity should be achieved?

Correlation between the anti –Xa level and bleeding has been established and reported by CDER. The target level of <30 ng/ml as representative of reduced bleeding was derived from dabigatran data and from indirect data from the Rocket trial of rivaroxaban; it appears to have been accepted by the treating community.

http://www.sciencedirect.com/science/article/pii/S075076581301023X

The andexanet data has further correlated anti XA levels (likely combined with anti TFPI effect) with ETP. Consequently, I believe that the proposed anti-XA level is a reasonable target endpoint.

The additional data required to further corroborate this surrogate for bleeding risk is clinical phenotype correlation, both (b) (4) ***, obtained either in pre-licensure trials (***(b) (4) ***) or from post-licensure observational cohorts.***

b) The adequacy of the observed duration of reversal. Please also comment on the duration of reversal that may be required to control bleeding and its relevance to the type of bleeding (for example, acute major GI bleeding, ICH, etc.) that is assessed in the ANNEX-4 study.

I did not see the efficacy results for control of major bleeding in the Annexa-4, other than ICH, in the dossier. Comparable major hemorrhage in severe congenital bleeding disorder patients depends on the location, potential consequences, rate of hemorrhage, and inciting/ ongoing stimulus for bleeding. In general, major hemorrhage is usually treated for at least 5-7 days and up to 10-14 days, except in ICH when treatment for 10-14 days is the norm. Of note, the precise data on duration of therapy is not available for these disorders so treatment duration is somewhat empiric. Replacement dose is often titrated downwards during that period at a rate commensurate with the bleeding response to therapy. However, treatment duration for such bleeding does not usually need to be titrated against the patient's endogenously elevated ETP and risk for serious of life threatening thrombosis. Consequently, the timelines would have to be commensurately shortened in the treatment of AC-related bleeding.

c) When considering the relevance of the duration of reversal, please comment on whether sufficient data exists (for example, based on the kinetics of bleeding and clot stability) to allow extrapolation of this data to support the adequacy of the duration of reversal to control bleeding.

See answer to 6(b)

d) The clinical significance of the observed rebound in anti-FXa activity for subjects anticoagulated with apixaban and rivaroxaban. Given the higher than placebo levels observed, please state whether additional premarket data are needed to evaluate this issue. ***The maintenance of ETP (potentially due to prolonged TFPI inhibition) in the normal range during this rebound period is reassuring. Of course, data on clinical risk of re-bleeding and re-thrombosis during the rebound period would provide further evidence with which to assess efficacy and safety and answer this question. However, a fundamental consideration with respect to pre-licensure burden of proof would be the assessment of this drug's safety and efficacy profile in comparison with the current standard of care for the treatment of major hemorrhage in these patients. Is there any evidence that andexanet would be less safe or efficacious than the current standard of care***?

e) Preliminary data for 35 subjects from the ANNEXA-4 trial intended to confirm the safety and clinical efficacy of the product in the target population indicate that the baseline levels of anti-FXa activity were in several instances much higher than those achieved just prior to andexanet dosing in the healthy volunteer phase 3 trials on which accelerated approval is being requested. In addition, Portola claimed that the phase 3 trials were designed to study the highest plasma concentration after the highest approved doses of apixaban and rivaroxaban. To what extent do higher baseline levels of anti-FXa activity observed in a subset of ANNEXA-4 subjects, compared to those in the healthy volunteer studies, impact our ability to extrapolate efficacy (in terms of the surrogate of anti-FXa activity reversal) to clinical hemostatic efficacy in the target population of patients with acute major bleeding?
http://eurheartj.oxfordjournals.org/content/ehj/early/2011/08/26/eurheartj.ehr342.full.pdf
Based on the above paper and additional literature, it would appear that moderate renal insufficiency patients with AF are at increased risk of bleeding and stroke compared

with renal-sufficient individuals, even at the lower recommended dosing of anti-Xa inhibitors. According to the demographic data for the ANNEXA -4 trial, 63% of subjects had renal insufficiency and 8-27% had higher than anticipated baseline anti XA levels resulting in < 50% rather than > 90% reduction in anti XA levels with andexanet standard dosing protocols. Extrapolation of healthy subject data for this sub-group of patients could be more problematic, although the clinical phase 3 trial data should indicate the extent to which this will be true. Dosing algorithms for this subgroup may need to be further optimized through either pre-licensure or post-licensure studies.

7. If the Agency were to consider approving the product for marketing purposes,

a. Is there sufficient data to support extrapolating the efficacy (adequate depth and duration of reduction in anti-FXa activity) to the class of Factor Xa inhibitor anticoagulants (which would also apply to anticoagulants in these classes that may be approved in the future). If there is insufficient data to support extrapolation to this class of inhibitors, is there sufficient data to demonstrate efficacy of andexanet in adequately (with regard to depth and duration) reversing the anticoagulant effect in each of the named FXa inhibitors (as measured through anti-FXa levels) to achieve hemostasis in patients who experience any or all types of anticoagulant related bleeding?

The data are consistent enough for PK/PD of immediate post- bolus reversal of anti-XA levels for all of the FXa inhibitors in the dossier for due consideration of class approval. However, the dose efficacy data is far more complete (bolus +infusion) for apixaban and rivaroxaban. For enoxaparin and endoxaban, the immediate reversal PK/PD is similar to apixaban and rivaroxaban. However, I remain unclear about what bolus dose/infusion recommendations would be made for endoxaban and enoxaparin based on the data presented.

b. For enoxaparin, please comment on whether the proposed surrogate endpoint of anti-FXa activity reversal is reasonably predictive of clinical benefit in the context of reversal of enoxaparin whose mechanisms of anticoagulation are not limited to FXa inhibition.
I would say that they are reasonably predictive with the caveats expressed above

8. For the ongoing confirmatory study, the Efficacy Analysis Population will only include subjects whose anti-FXa activity is >75 ng/mL, which Portola states corresponds to approximately twice the anti-FXa level achieved at 24 hours after administration of the highest approved doses for rivaroxaban and at 12 hours for apixaban. Please comment on the acceptability of this threshold; for example, as it relates to the degree of anticoagulation that would be expected to aggravate bleeding.
See response to 6e. I agree with your point. In many cases (60%), plasma levels of anti-Xa activity would exceed the expected in individuals who are at the highest risk for major bleeding – i.e., in the elderly and in those with moderate renal compromise. For that reason, the Efficacy Analysis Population should include all levels in the ANNEXA4 study.

9. Preliminary data from the confirmatory study show that 63% (22/35) of subjects requiring urgent reversal have impaired renal function (eGFR <60 mL/min/1.73 m2). The safety data in these subjects has been provided within the discussion of the summary of the Phase 3b/4 study. The safety of andexanet in renally impaired subjects has not been evaluated in the healthy volunteer studies. Please state if additional premarket studies are required to evaluate the safety of the product in this population.
Yes- see above responses

10. Portola has developed assays to detect anti-drug antibodies that may bind endogenous coagulation Factors X and Xa, and no such antibodies were found. However, Portola did not develop assays to study antibodies that can neutralize activity of factors X and Xa.

Interference of neutralizing antibodies to factors X and Xa with the pharmacodynamics and pharmacokinetics assays (e.g., prothrombin time and anti-fXa activity) was not evaluated either. Please comment on the risk for immunotoxicity and potential for andexanet to elicit binding and/or neutralizing antibodies to endogenous Factor X or Factor Xa.

The risk of immunogenicity with FX replacement in FX-deficient patients is quite low and best explained by vitamin K protein homology. The extent to which this molecule differs in homology and the fact that it is a recombinant modified protein may increase the risk beyond that of endogenous or plasma –derived replacement protein. If it mimics other replacement proteins, the risk would likely manifest with repeated or prolonged exposure to the non-native protein in the presence of immune danger signals. This risk is unlikely to be captured in pre-licensure studies but will require careful post-licensure surveillance.

11. Given the evidence of prolonged procoagulant anti-TFPI effect of andexanet, do you have additional recommendations with regard to timing of re-initiation of anticoagulation (either bridging or with fXa inhibitors) in the ongoing ANNEX 4 confirmatory study? Is the incidence of thrombotic events noted in the 35 subjects in the ongoing ANNEX 4study consistent with the expected rate of such events in this at-risk population?

I cannot evaluate the comparative incidence and believe that the timing or re-anticoagulation would have to be patient specific and contingent on comparative risk of re-bleeding and re-thrombosis.

12. Preliminary data from the ongoing confirmatory study show that bleeding patients will have relatively low anti-fXa levels and normal thrombin generation assay values at the time of andexanet administration, and therefore will be exposed primarily to the anti-TFPI rather than anti-fXa activity of andexanet. Please comment on the safety and efficacy of TFPI inhibition in this at-risk population.

I don’t totally understand the question, given the summary data of anti-XA activity at the time of bolus infusion, as presented in the dossier. In any case, the risk needs to be calculated against that of morbidity and mortality related to major bleeding