Reversal of Betrixaban-Induced Anticoagulation in Healthy Volunteers by Andexanet Alfa

Mark Crowther; Genmin Lu; Janet Leeds; Joyce Lin; Alex Gold; Stuart Connolly; John Curnutte; Mark J. Alberts MD FAHA; Pamela B. Conley

McMaster University, Hamilton, ON, Canada; Portola Pharmaceuticals, Inc., South San Francisco, CA, USA

2017 ANNUAL MEETING
BOSTON, MASSACHUSETTS
OCTOBER 7–11, 2017

Introduction

- Andexanet alfa (andexanet) is a modified, recombinant human factor Xa (FXa) that acts as a decoy to bind and sequester FXa inhibitors, thus reversing their anticoagulation effects [1-3].
- Betrixaban has been approved by the FDA for extended (35 to 42 days) prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness and at risk for VTE [4].

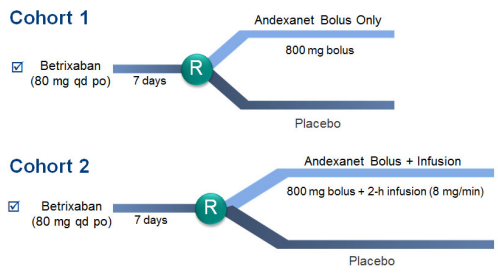
Objective

- To analyze the efficacy of andexanet in reversing the anticoagulant activity of betrixaban in healthy volunteers.

Methods

- In this Phase 2, randomized, double-blind study, healthy subjects were dosed with 80 mg qd po betrixaban to steady state (7 days) **(Figure 1)**.
- In Cohort 1, subjects (n=6) received 800-mg andexanet bolus 3 h after the last dose of betrixaban, or matching placebo (n=3).
- In Cohort 2, subjects (n=6) received 800-mg andexanet bolus 4 h after the last betrixaban dose, followed immediately by a 2-h andexanet infusion (8 mg/min), or matching placebo (n=3).
- Study endpoints included assessments of safety and pharmacodynamic markers of anticoagulation reversal.

Figure 1. Study Design



Results

- Andexanet rapidly (2 min after the bolus) decreased anti-FXa activity by ~80% in Cohorts 1 and 2 ($p<0.001$ vs. placebo) **(Figure 2)**.
- Following andexanet administration, unbound (pharmacologically active) betrixaban plasma concentration rapidly decreased by 73% and 83% in Cohorts 1 and 2, respectively ($p<0.001$ vs. placebo) **(Figure 3)**.
- The effects in anticoagulation markers (anti-FXa activity and unbound betrixaban levels) were maintained during the 2-h infusion of andexanet.

Figure 2. Anti-FXa Activity

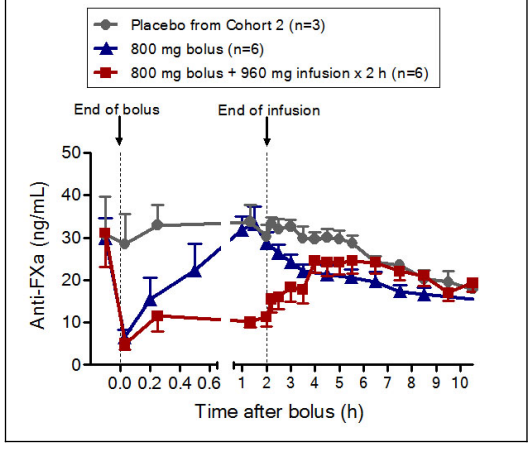
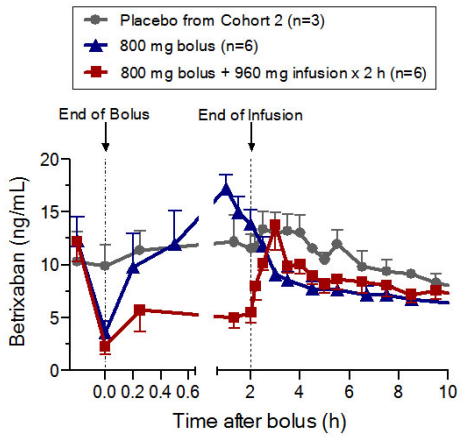
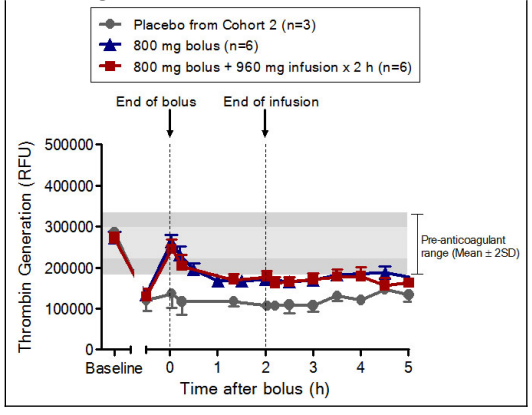


Figure 3. Unbound Betrixaban Plasma Levels



- In total, thrombin generation was restored in 11/12 (91.7%) subjects administered andexanet vs. 2/6 (33.3%) placebo subjects **(Figure 4)**.
- Restoration of thrombin generation was defined as within the mean pre-anticoagulant value ± 2 standard deviations (SD)

Figure 4. Thrombin Generation



Safety

- Andexanet was well tolerated, there were no serious or severe adverse events, and no subjects discontinued from the study.
- There were no thromboembolic events.
- There were no neutralizing antibodies to andexanet or antibodies against endogenous FX or FXa.

Conclusions

- Andexanet was well-tolerated and rapidly reversed anticoagulation effects of betrixaban in healthy subjects.
- The results of this and other studies in healthy subjects indicate tindicate that andexanet has the potential as a universal antidote for FXa inhibitors.
- An ongoing Phase 3b/4 study (ANNEXA-4) study in patients receiving a FXa inhibitor who present with acute major bleeding and require urgent reversal of anticoagulation will provide clinical efficacy and safety information on andexanet in this population [5,6].

References

1. Lu G et al. Nat Med 2013;19:446-51.
2. Lu G et al. J Thromb Haemost. 2017;Jul 6 [Epub ahead of print].
3. Siegal D et al. N Engl J Med. 2015;373:2413-24.
4. Betrixaban (Bevyxxa) Prescribing Information. June 2017.
5. Connolly S et al. New Engl J Med. 2016;375:1131-41.
6. Connolly S et al. New Engl J Med. 2016;375:2499-500.