Edoxaban Effects on Bleeding Following Punch Biopsy and Reversal by a 4-Factor PCC

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Background

- Edoxaban is an orally active, selective inhibitor of factor Xa approved in Japan for the prevention of stroke in AF, treatment and prevention of recurrent VTE, and prevention of VTE following orthopedic surgery.
- Edoxaban is currently under regulatory consideration in other countries.
- There are currently no specific reversal agents for NOACs.
  - The effects of edoxaban on ETP, but not PT, were reversed by a 3-factor PCC at 25 and 50 IU/kg.
  - The effects of rivaroxaban on PT and ETP were reversed by a 4-factor PCC at a dose of 50 IU/kg.
  - The effects of edoxaban on PT were partially reversed by a 4-factor PCC in vitro.
- It is unclear which biomarkers of coagulation best correlate with bleeding.
- Standard bleeding time assays are insensitive to edoxaban-mediated anticoagulation effects.

AF, atrial fibrillation; ETP, endogenous thrombin potential; NOAC, non-vitamin K oral anticoagulant; PCC, prothrombin complex concentrate; PT, prothrombin time; VTE, venous thromboembolism.

2. Brown K et al. JACC. 2014; 63(12 Suppl 1): A2095
Objective

- To evaluate the reversal of the effect of a single 60-mg edoxaban dose by a 4F-PCC as measured by:
  - Punch biopsy bleeding duration (BD) – primary endpoint
  - Punch biopsy bleeding volume (BV)
  - Endogenous thrombin potential (ETP), a parameter of thrombin generation assay
PART 1*

- Established punch biopsy method
- BD and BV correlated with edoxaban exposure (60 and 180 mg)

PART 2

- Assessed reversal of edoxaban effect following 4F-PCC

*results not reported in this presentation

BD, bleeding duration; BV, bleeding volume; 4F-PCC, 4-factor prothrombin complex concentrate
**Study Design: Part 2**

- Double-blind, 2-treatment, 2-way crossover design with sequential descending 4F-PCC dose cohorts
  - A total of 22 evaluable subjects per cohort was required in order to have 80% power to demonstrate the 95% CI for the BD ratio (post 4F-PCC treatment/baseline) to be within a 70% to 143% limit
  - Testing was to continue until identification of a 4F-PCC dose that clearly did not attain complete reversal
  - BD was selected as the primary endpoint based on lower variability than BV as determined in Part 1

**BD, bleeding duration; BV, bleeding volume; CI, confidence interval; 4F-PCC, 4-factor prothrombin complex concentrate**
Results

**Population:**
- Subject characteristics were comparable between 3 different 4F-PCC dose cohorts
  - The majority of the randomized subjects were white (n = 64; 58.2%) and male (n = 77; 70%)
  - Mean subject age was 30.4 years, mean weight was 75.9 kg, and mean BMI was 25.0 kg/m²

**Pharmacokinetics:**
- Pharmacokinetic parameters of edoxaban were consistent with previous studies
- Pharmacokinetic parameters of 4F-PCC components were consistent with previous studies

BMI, body mass index; 4F-PCC, 4-factor prothrombin complex concentrate
All subjects received edoxaban 60 mg prior to 4F-PCC infusion.

ETP, endogenous thrombin potential; 4F-PCC, 4-factor prothrombin complex concentrate

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### Bleeding Duration

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<th>4F-PCC dose (IU/kg)</th>
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<td><strong>4F-PCC</strong></td>
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### Bleeding Volume

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<tr>
<td><strong>4F-PCC</strong></td>
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</table>
All subjects received edoxaban 60 mg prior to 4F-PCC infusion.

BD, bleeding duration; BV, bleeding volume; ETP, endogenous thrombin potential; 4F-PCC, 4-factor prothrombin complex concentrate; PT, prothrombin time

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**Reversal Effects**

<table>
<thead>
<tr>
<th>4F-PCC Dose (IU/kg)</th>
<th>BD (min)</th>
<th>ETP (nM*min)</th>
<th>PT (sec)</th>
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<tr>
<td>50</td>
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Percent Reversal Post-infusion of 4F-PCC (Baseline and Placebo Corrected)

Complete Reversal
Pharmacodynamics Time Courses

ETP, endogenous thrombin potential; PT, prothrombin time; 4F-PCC, 4-factor prothrombin complex concentrate

Bar indicates 4F-PCC infusion (minimum duration of 15 minutes)
Safety

- No serious AEs occurred
- One AE led to early discontinuation
  - Mild injection site phlebitis; not related to the study drug
- Most AEs were mild
- Edoxaban and 4F-PCC were well tolerated in this study

AE, adverse event; 4F-PCC, 4-factor prothrombin complex concentrate
Conclusions

- 4F-PCC reversed the prolongation of BD by edoxaban in a dose-dependent manner
- Effects on ETP correlate well with BD and BV reversal
  - 4F-PCC 50 IU/kg fully reversed ETP by 30 minutes post-infusion
  - At later time points following 4F-PCC infusion, ETP increased above baseline in a dose-dependent manner, possibly due to prothrombin complex factors present in the 4F-PCC
- PT was only partially reversed even at the highest dose of 4F-PCC and does not correlate well with BD reversal
- Treatment with edoxaban alone or with 4F-PCC was safe and well tolerated by healthy male and female subjects in this study
- A dose of 50 IU/kg 4F-PCC appears to reverse the activity of a therapeutic dose of edoxaban

BD, bleeding duration; BV, bleeding volume; ETP, endogenous thrombin potential; 4F-PCC, prothrombin complex concentrate; PT, prothrombin time
The authors would also like to thank the subjects who participated in the study.
TGA – Peak Thrombin

Bar indicates 4F-PCC infusion (minimum duration of 15 minutes)
TGA, thrombin generation assay; 4F-PCC, 4-factor prothrombin complex concentrate
TGA – Lag Time

Bar indicates 4F-PCC infusion (minimum duration of 15 minutes)
TGA, thrombin generation assay; 4F-PCC, 4-factor prothrombin complex concentrate
Bar indicates 4F-PCC infusion (minimum duration of 15 minutes)
TGA, thrombin generation assay; 4F-PCC, 4-factor prothrombin complex concentrate
TGA – Velocity Index

Bar indicates 4F-PCC infusion (minimum duration of 15 minutes)
TGA, thrombin generation assay; 4F-PCC, 4-factor prothrombin complex concentrate
Bar indicates 4F-PCC infusion (minimum duration of 15 minutes)
4F-PCC, 4-factor prothrombin complex concentrate