Small Molecule Antidote for Anticoagulants

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Disclosures

• Bryan Laulicht, Sasha Bakhru, Connie Lee, Christopher Baker, Xuan Jiang, James Costin and Solomon Steiner are employees of Perosphere Inc.

• Edith Mathiowitz is a consultant of Perosphere Inc.

• All of the Authors own shares and/or options in Perosphere Inc.
Introduction

- PER977 is a synthetic small molecule
- As demonstrated by dynamic light scattering (DLS), PER977 directly binds all approved new oral anticoagulants (NOACs):
  - Dabigatran, rivaroxaban, apixaban and edoxaban
- Completed 14 day repeat dose PER977 i.v. two species (dog and rat) toxicology study shows no significant adverse events
- Completed safety study with PER977 + rivaroxaban and PER977 + dabigatran showing no significant adverse events in beagle dogs
- Completed metabolite identification
- No CYP inhibition or metabolism in vitro
- Expected to be in clinical trials in Q1 2013
PER977-apixaban dynamic light scattering (DLS) binding

- PER977 binds apixaban at a mass ratio of 1:1 :: PER977:apixaban
PER977 competitively binds new oral anticoagulants (NOACs) restoring blocked coagulation factor activity.

**Anticoagulation:** Factor Xa or IIa activity inhibited by NOAC

**Reversal:** Factor Xa or IIa activity restored when PER977 binds NOAC
Overview

PER977:

- Reduces blood loss and bleeding time, reversing the anticoagulant activity of dabigatran, rivaroxaban, apixaban and edoxaban in rat tail transection and incision assays
- Reversal confirmed by aPTT and Xa assays in human blood ex vivo
- PER977 alone has no dose-dependent effect on coagulation (by platelet aggregation or TEG) ex vivo
- Presence of rivaroxaban or dabigatran delays PER977 metabolism and increases the MTD of PER977 in blood serum (rats)
12.5mg PER977 reduces blood loss in dabigatran (15mg p.o.) treated rats to normal levels

- Full reversal at a dose mass ratio of 0.83:1, N=3 **p<0.01 ***p<0.001
12.5mg PER977 reduces blood loss in rivaroxaban (2mg p.o.) treated rats to normal levels

- Full reversal at a dose mass ratio of 6.25:1, N=3 *p<0.05
5mg PER977 reduces blood loss in apixaban (1.25mg p.o.) treated rats to normal levels

- Full reversal at a dose mass ratio of 4:1, N=3 ***p<0.001
PER977 (12.5 mg) reduces blood loss in edoxaban (5 mg p.o.) treated rats to normal levels

- Full reversal at a dose mass ratio of 2.5:1, N=5 **p<0.01, ***p<0.001
PER977 dabigatran reversal is confirmed by a rat tail incision bleeding time model

** p<0.01, *** p<0.001 compared to PER977 group

## p<0.01, ### p<0.001 compared to baseline (pre-dose bleeding time)
APTT testing confirms PER977 reverses rivaroxaban in fresh human whole blood *ex vivo*
PER977 restores Factor Xa activity in a dose-dependent fashion ex vivo in human plasma

PER977 restores Xa activity to an effective rivaroxaban concentration below MEC

Effective rivaroxaban concentration

218μg/L rivaroxaban

218μg/L rivaroxaban, 1.25μg/L PER977

218μg/L rivaroxaban, 12.5μg/L PER977

218μg/L rivaroxaban, 125μg/L PER977

218μg/L rivaroxaban, 1,250μg/L PER977
PER977 alone shows no dose-dependent effects on platelet aggregation in human blood ex vivo.
PER977 alone shows no dose-dependent effects on thromboelastography (TEG) *ex vivo*. 

![Graphs showing no dose-dependent effects on TEG parameters](image)
Metabolism of PER977 occurs in the blood

Metabolism of PER977 in the blood is slowed in the presence of new oral anticoagulants (NOACs)
NOAC increases the clearance half-life of PER977 in blood serum

- PER977-NOAC complex is protected from enzymatic metabolism
NOAC increases the maximally tolerated dose (MTD) of PER977 in rats

- Toxicologic effects of high doses of PER977 are reduced in the presence of NOAC, further evidencing complex formation.
Review

PER977 is a synthetic small molecule that:

- Reduces blood loss and bleeding time, reversing the anticoagulant activity of dabigatran, rivaroxaban, apixaban and edoxaban in rat tail transection and incision assays
- Reversal confirmed by aPTT and Xa assays in human blood ex vivo
- PER977 alone has no dose-dependent effect on coagulation
- Presence of rivaroxaban or dabigatran delays PER977 metabolism in blood serum and increases the MTD of PER977 (rats)
- Completed 14 day repeat dose PER977 i.v. two species (dog and rat) toxicology study shows no significant adverse events
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- No CYP inhibition or metabolism in vitro
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Thank you!

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