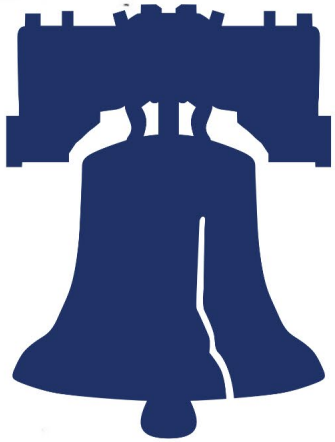


ISTH VIRTUAL CONGRESS
2021 JULY 17–21
ISTH2021.ORG
HOSTED FROM PHILADELPHIA
SCIENCE CONQUERING DISEASE

Orally Delivered Factor VIII Restores Hemostasis in a Hemophilia A Dog

Mir A. Hashim[1], Alyson Yamaguchi[1], April T. Vo[1], Arvinder K. Dhalla[1], Baber Syed[1], Leonard Fung[1], Vasudha Salgotra[1], Anvesh Dasari,[1] Gerald Schrenk[2], Oliver Zoechling[2], Dan Sexton[3], Geoffrey Allen[3], Charles T. Long[4], Elizabeth P. Merricks[4], Mir Imran[1], **Timothy C. Nichols[4]**

[1]Rani Therapeutics, San Jose, CA; [2]Takeda Pharma GmbH, Orth, Austria; [3]Takeda Pharmaceuticals USA Inc., Cambridge, MA; [4]University of North Carolina, Chapel Hill, NC

ISTH 2021 VIRTUAL CONGRESS

Disclosures for Timothy C. Nichols

In compliance with COI policy, ISTH requires the following disclosures to the session audience:

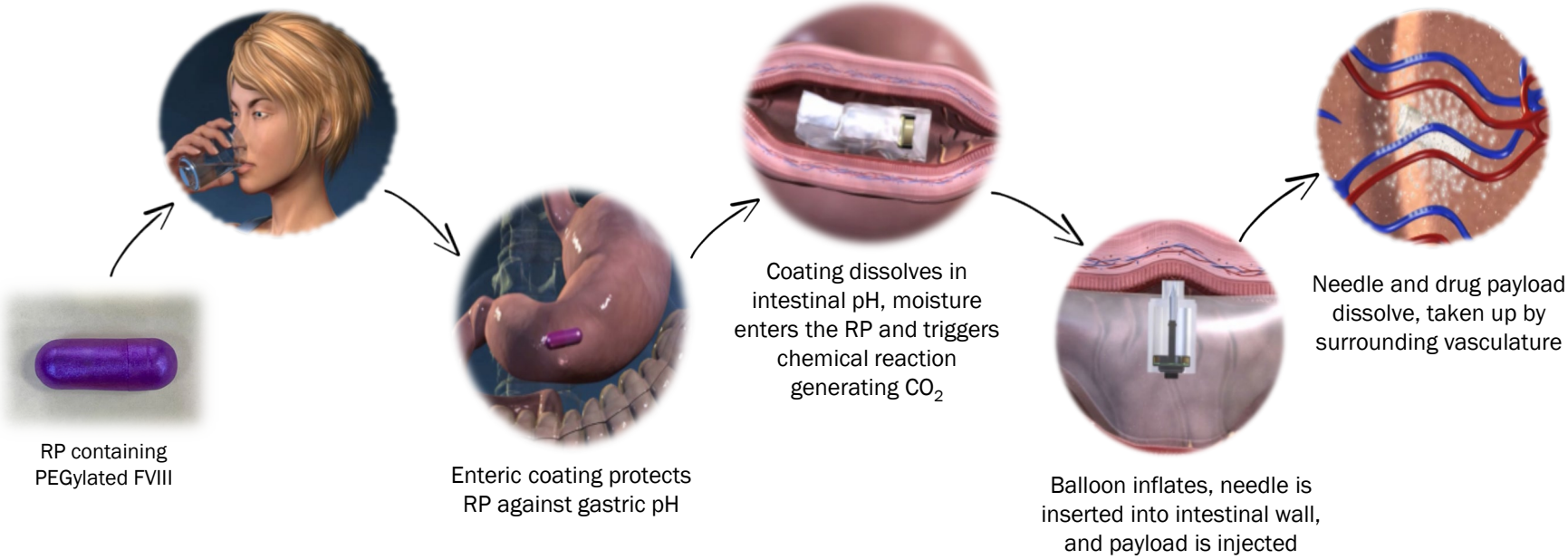
Research Support/P.I.	Research Support from Rani Therapeutics / Takeda Pharmaceuticals
Employee	No relevant conflicts of interest to declare
Consultant	No relevant conflicts of interest to declare
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Honoraria	No relevant conflicts of interest to declare
Scientific Advisory Board	No relevant conflicts of interest to declare

Development of an Oral FVIII Therapy

- People with hemophilia A face lifelong burden of frequent IV injections
- Development of an oral FVIII therapy could greatly improve compliance and quality of life for people with hemophilia A
- A novel orally ingestible “robotic pill” has been designed to deliver biologics similar to parenteral injections[1]
- This platform was used to deliver FVIII orally to a hemophilia A dog

[1]Dhalla et al: A robotic pill for oral delivery of biotherapeutics: safety, tolerability, and performance in healthy subjects. *Drug Deliv Transl Res 2021* https://doi.org/10.1007/s13346-021-00938-1

Robotic Pill (RP) Technology



https://www.ranitherapeutics.com/technology/

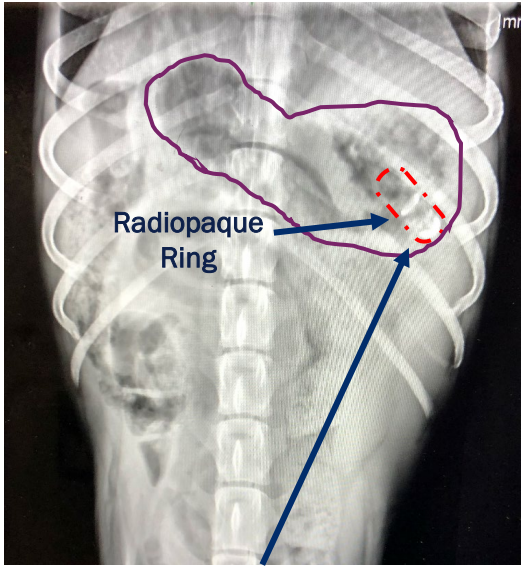
ISTH 2021

Study Design

- **Aim:** Evaluate safety and efficacy of delivering FVIII via orally ingestible robotic pill (RP) in the hemophilia A dog model
- **Methods:**
  - Hemophilia A dog (16.8 kg) ingested a single oral RP containing 2,650 IU PEGylated human recombinant FVIII (approximately 150 IU/kg)
  - Serial blood sampling collected up to 7 days to assess pharmacokinetic (PK) and pharmacodynamic (PD) parameters
    - FVIII Antigen, FVIII Activity, Activated partial thromboplastin time (aPTT), Whole blood clotting time (WBCT) and thromboelastogram (TEG)
  - Data were compared to two hemophilia A dogs that received an equivalent dose either via direct intraperitoneal (IP) or intravenous (IV) injection

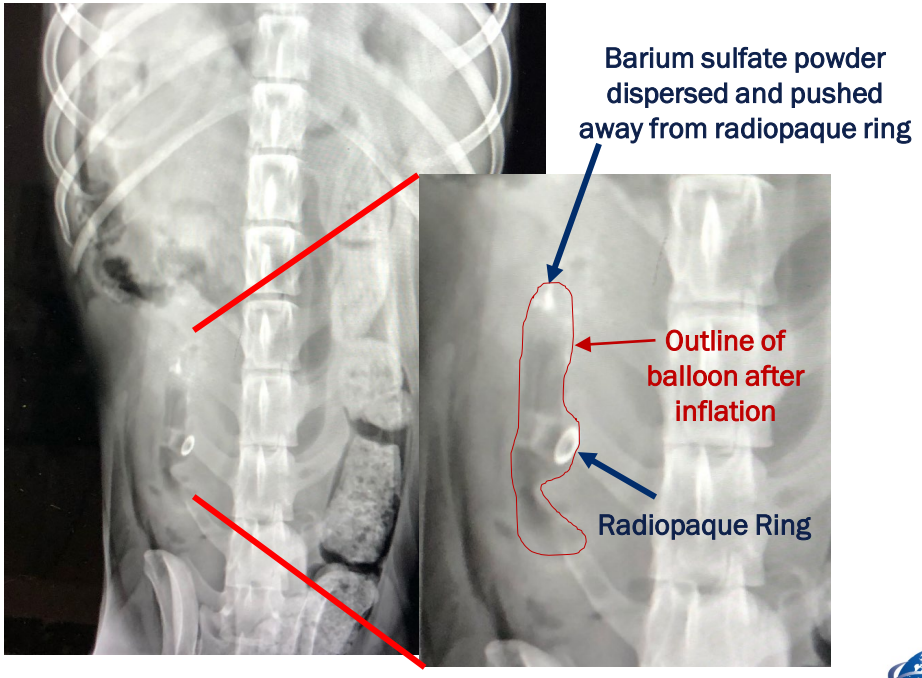
Radiographic Tracking of the RP in Hemophilia A Dog

Intact RP in Stomach



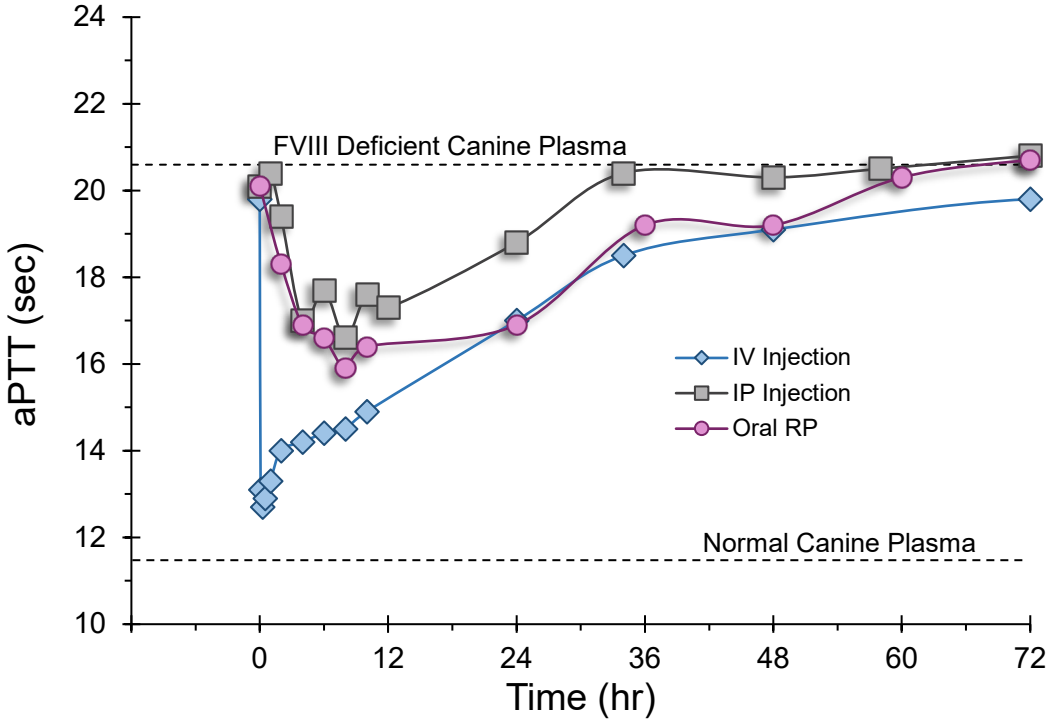
Barium sulfate powder outside of device, within capsule shell

RP Deployed in Small Intestine

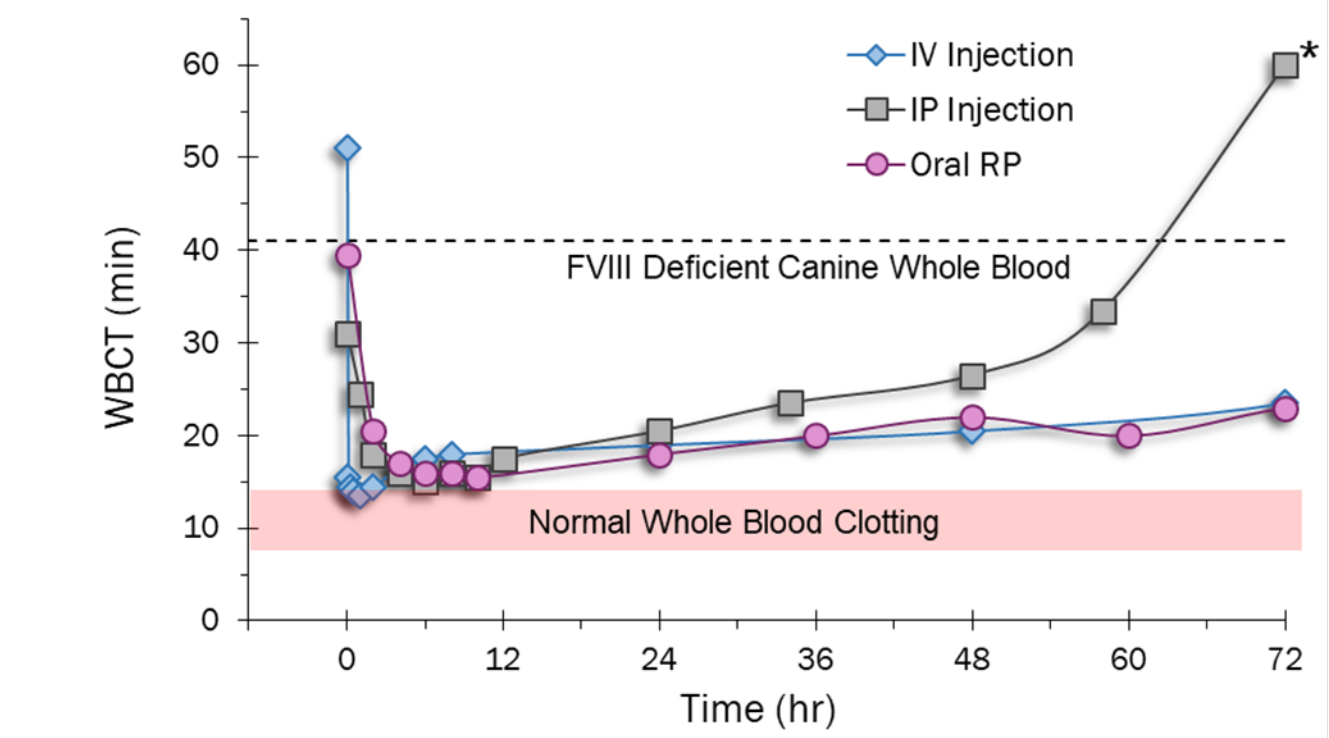


ISTH 2021

Oral RP, IP, and IV Injections of PEG-FVIII (~150 IU/kg) Shortened the aPTT Values



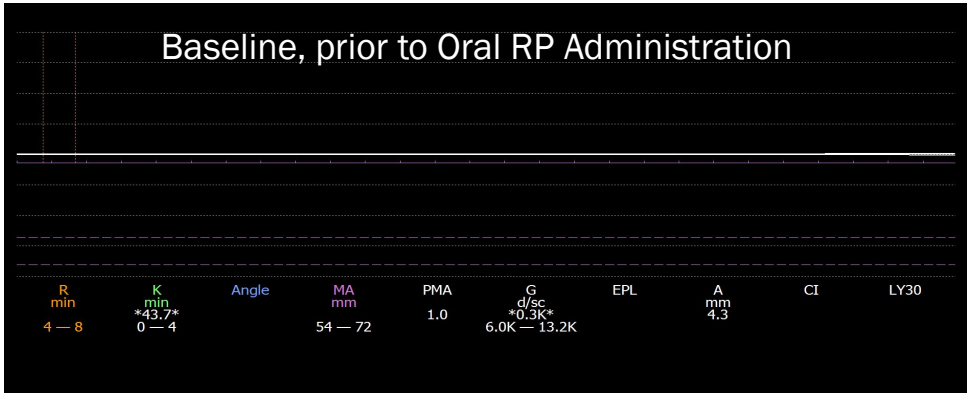
Oral RP, IP, and IV Injections of PEG-FVIII (~150 IU/kg) Shortened the WBCT

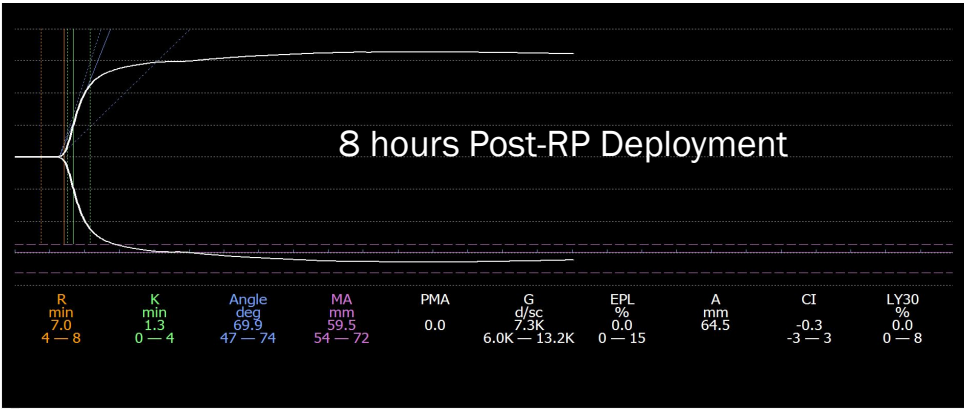


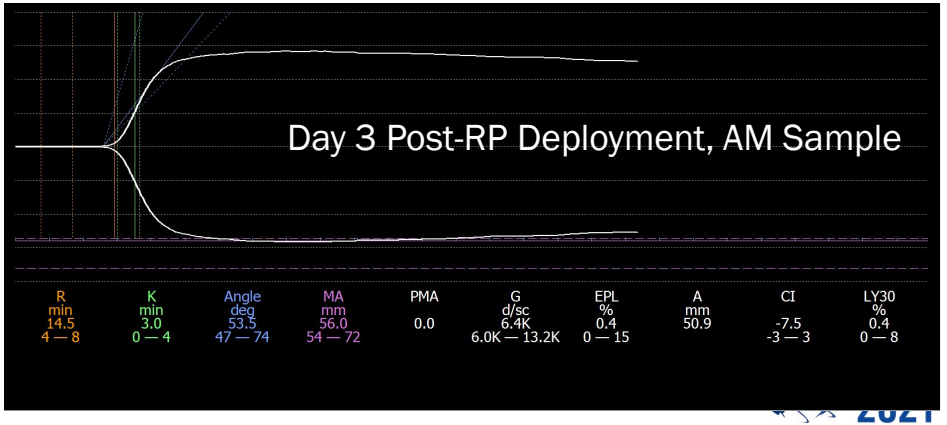
*Abrupt truncation of the effect of FVIII administered via IP injection due to the formation of neutralizing antibodies.

ISTH 2021

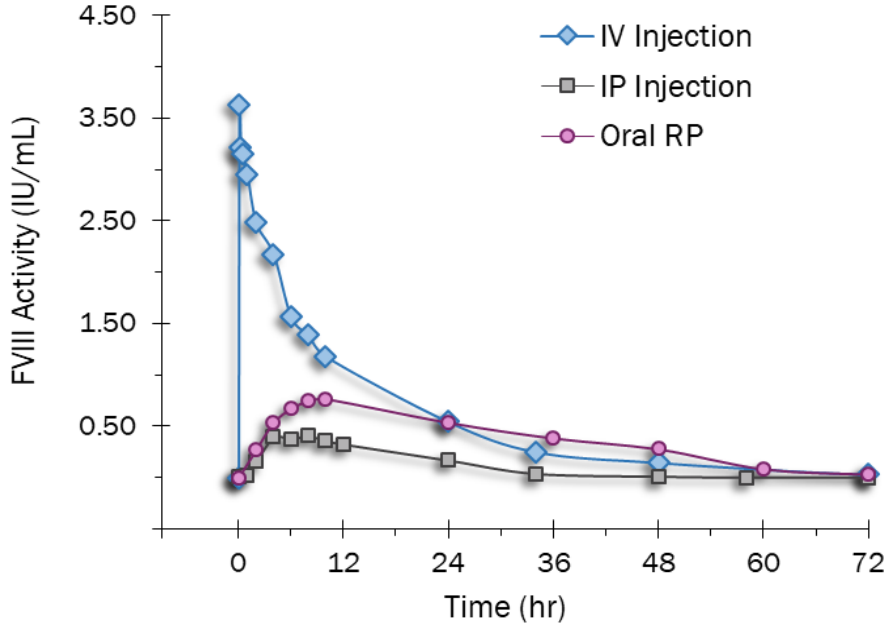
Oral RP (PEG-FVIII, ~150 IU/kg) Corrects Abnormal TEG Values







FVIII Activity Levels Achieved by Oral RP, IP, and IV Administration of PEG-FVIII

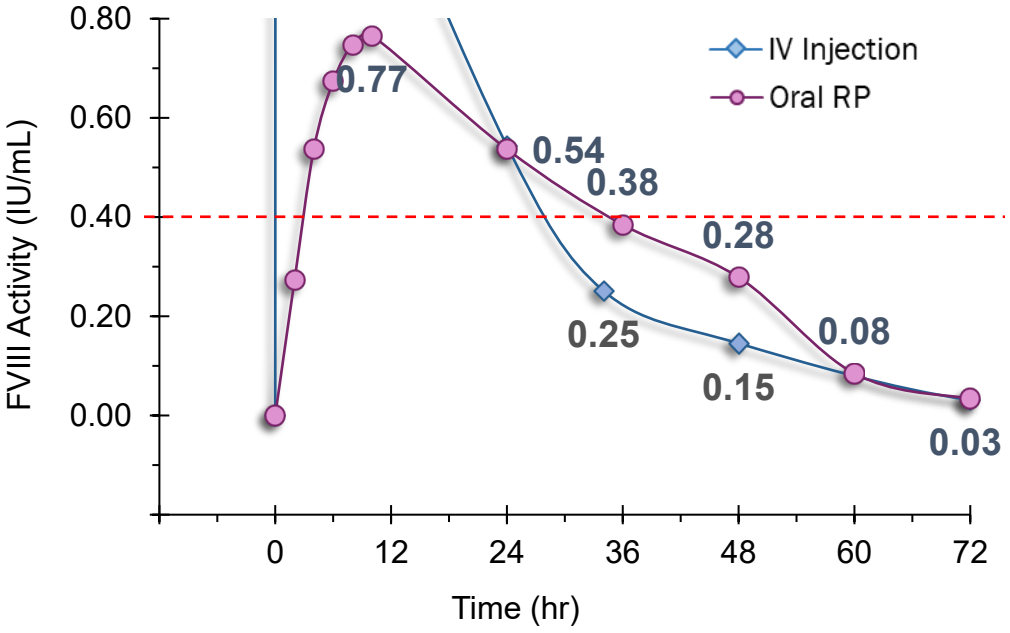


Treatment	C_{max} (IU/mL)	T_{max}	AUC ((IU/mL).hr)	F (%)
IV Injection	3.63	5 min	42	100
IP Injection	0.41	8 h	*	*
Oral RP	0.77	10 h	28	67

*Animal receiving IP injection developed neutralizing antibodies by Day 5, therefore AUC and bioavailability (F) could not be reliably computed for the IP route

Pharmacokinetic Data Suggest That Daily Oral RP Can Maintain FVIII Levels ≥40%

FVIII activity plots showing trough levels

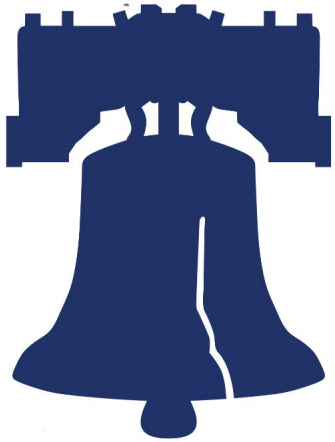


- IV PEGylated FVIII given every 3 days provides trough levels of 1-3%
- **Daily oral dosing with Oral RP could potentially provide trough levels at ≥ 40%**
- This dosing regimen may provide protection against spontaneous bleeds, possibly at even lower oral daily doses

Summary

- A single dose of PEGylated FVIII delivered via Oral RP restored hemostasis in the hemophilia A dog model
- The bioavailability of PEGylated FVIII delivered via Oral RP was 67%
- PK-PD analyses indicate FVIII was delivered by the Oral RP into the peritoneal space

These data provide early preclinical proof-of-concept of the potential to replace intravenous FVIII therapy with an orally ingestible therapy for people with hemophilia A



ISTH 2021 VIRTUAL CONGRESS
JULY 17–21
ISTH2021.ORG
HOSTED FROM PHILADELPHIA
SCIENCE CONQUERING DISEASE

Thank you!

ISTH 2021 VIRTUAL CONGRESS