Use of Topical Elastase to Reduce AV Fistula Failure

C. Keith Ozaki, M.D.
John A. Mannick Professor of Surgery
Brigham and Women's Hospital/Harvard Medical School

Disclosures
- Unrestricted Gift from Smith and Nephew, Inc.
- Joint Research Projects with Novartis Institutes for Biomedical Research, Inc.
- DSMB for Neograft, Inc.
- Scientific Consultant for Proteon Therapeutics, Inc.

Elastin Fibers in Vein

Intima
Media
Adventitia

- Internal elastic lamina
- Black elastin fibers

Vonapanitase
- Investigational recombinant human chymotrypsin-like elastase family member 1
- Expressed in human dermis; Protease that cleaves peptide bonds in elastin
- Elastin fragments known to be chemotactic for the cells that cause intimal hyperplasia
- Fast Track designation in the US; Orphan Drug designation in the US and EU for AVFs

Vonapanitase Administration
- Single treatment applied topically to adventitial surface immediately after AVF creation
- Delivered as a series of drops over 10 minutes
- Irrigation of surgical site with saline lavage after treatment
- Inactivated by blood
Green = elastin autofluorescence; Blue = PRT-201 fluorescence

### Vonapanitase Adheres to Elastic Fibers in Human Cephalic Vein Adventitia

Pre-treatment

Post-treatment (30 µg dose, 10 min)

### Pre-clinical Evidence Suggesting Mechanism of Action

- Peptide fragments of elastin are recognized by cells implicated in intimal hyperplasia
- Porcine elastase inhibits cell migration to intima and reduces intimal hyperplasia
- Vonapanitase and a porcine homologue deceased intimal hyperplasia in outflow vein of a rabbit AVF model


### Vonapanitase AVF Phase 2 Data

**Design**
- Randomized, double-blind, placebo-controlled (NCT01305824)

**Patients**
- 151 treated pre-dialysis or hemodialysis Radiocephalic or brachiocephalic AVF

**Doses**
- Placebo, 10, and 30 mcg (1:1:1)

**Endpoints**
- Primary: Primary Unassisted Patency (time to thrombosis or first procedure)
- Secondary: Unassisted Maturation, Secondary Patency, Usability and AVF Stenosis

**Timing**
- 3+ years of follow-up

Early Dis: Hye et al, JV 2014

### Primary Unassisted AVF Patency

- **30 mcg group (n=49)**
- **10 mcg (n=51)**
- **Placebo (n=51)**

- Vonapanitase reduced the risk of primary patency loss by 37%
- The proportion without patency loss increased from 36% to 50%

1. 30 mcg group - All AVFs. Hazard ratio 0.63 (Log-rank, p=0.10)

### Primary Unassisted Patency In Radiocephalic AVFs

- **30 mcg group (n=20)**
- **10 mcg (n=23)**
- **Placebo (n=24)**

- Vonapanitase reduced the risk of primary patency loss by 63%
- The proportion without patency loss increased from 31% to 63%

1. Not pre-specified

1. 30 mcg group – RC AVFs. Hazard ratio 0.37 (Log-rank, p=0.02)
Unassisted AVF Maturation

Definition of Unassisted Maturation
- Vein lumen diameter ≥ 4 mm and blood flow volume ≥ 500 mL/min at 3 months without requiring a corrective procedure

Results
- Approximate doubling in unassisted maturation rate for RC AVFs (30 mcg)

Secondary Patency--Radiocephalic

Vonapanitase reduced the risk of secondary patency loss by 76%.

The proportion without patency loss increased from 59% to 90%.

Procedure Rates to Restore/Maintain Patency

Definition of Procedure Rate: # of days (per patient per year) in which patient underwent a procedure to restore/maintain patency

Vonapanitase reduced the procedure rate 69% in Cimino patients

AVF Use for Hemodialysis

Definition of AVF Use for HD: ≥ 90 days of consecutive use of the AVF, independent of the need for procedures to restore or maintain patency

Results
- The proportion with RC AVF use increased nonsignificantly from 56% to 80%

Design of Phase 3 “PATENCY” Trials:

- Randomized, double-blind, placebo-controlled
- 300 patients in U.S., Radiocephalic AVFs
- 12 months of follow-up
- Vonapanitase 30 mcg vs. placebo (2:1)

Design of Phase 3 “PATENCY” Trials: Endpoints Same as Phase 2

- Randomized, double-blind, placebo-controlled
- 300 patients in U.S., Radiocephalic AVFs
- 12 months of follow-up
- Vonapanitase 30 mcg vs. placebo (2:1)
- Primary: Primary Unassisted Patency
- Secondary: Secondary Patency
- Tertiary: Unassisted Maturation, Rate of Procedures, Use for Hemodialysis
**Vonapanitase Phase 3 Status**

- **PATENCY-1**
  - Fully enrolled in October, 2015
  - Top-line data available in December, 2016

- **PATENCY-2**
  - Actively enrolling
  - Anticipate fully enrolled in Q1, 2017

---

**Other Potential Vascular Applications Beyond AVFs**

- Endovascular Balloon Angioplasty Adjunct (access, venous, vein graft)

**Vonapanitase data to date supports (in radiocephalic AVFs)**

- Improved AVF maturation
- Increased primary unassisted patency
- Fewer corrective procedures to restore/maintain AVF patency
- Increased secondary patency

Potentially transformative novel adjunct to enhance hemodialysis fistula maturation