
BRIGHAM HEALTH
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WOMEN'S HOSPITAL
Vonapanitase to Increase Fistula Use for Hemodialysis and Secondary Patency—Pivotal Trial Results
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TEACHING HOSPITAL
A FOUNDING MEMBER OF PARTNERS HEALTHCARE
PROTEON
THERAPEUTICS

Disclosures

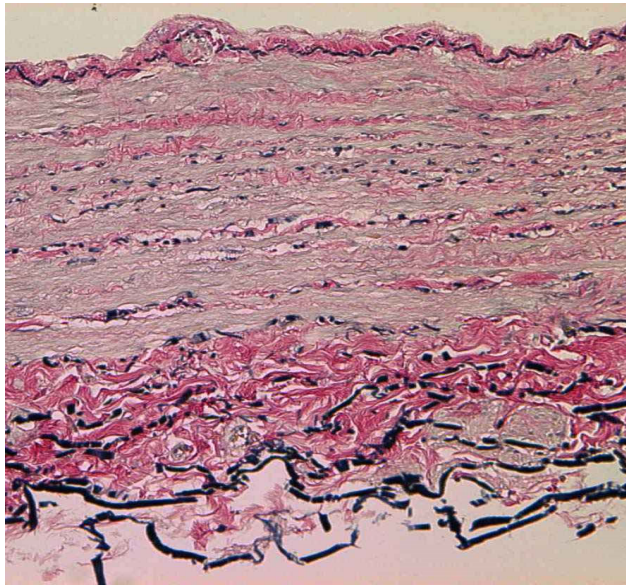
- Consultant: Proteon Therapeutics, Humacyte, Merck Sharp & Dohme, Medtronic, Semma Therapeutics

- Slide Content for unpublished data largely supplied by Proteon Therapeutics

PROTEON THERAPEUTICS

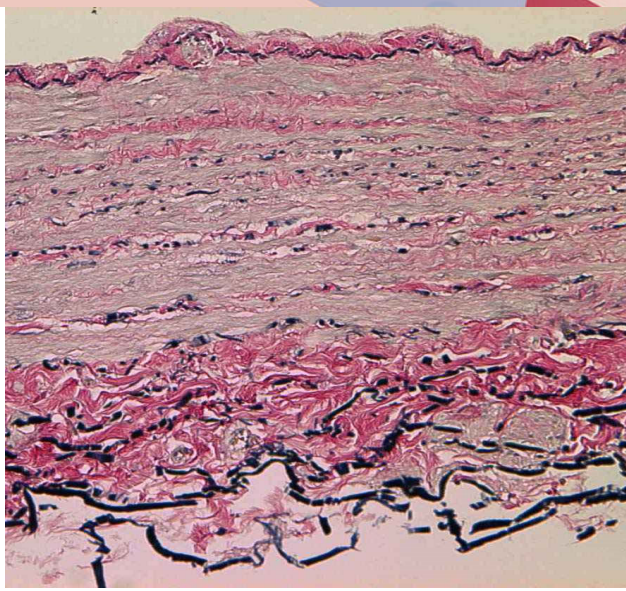
Investigational Recombinant Human Elastase

- Vonapanitase—cleaves elastin peptide bonds



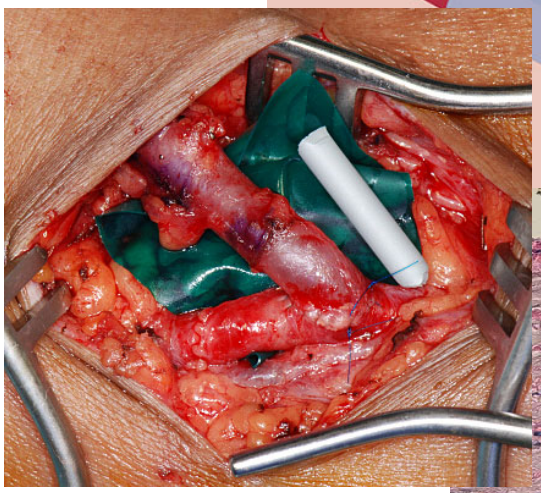
Investigational Recombinant Human Elastase

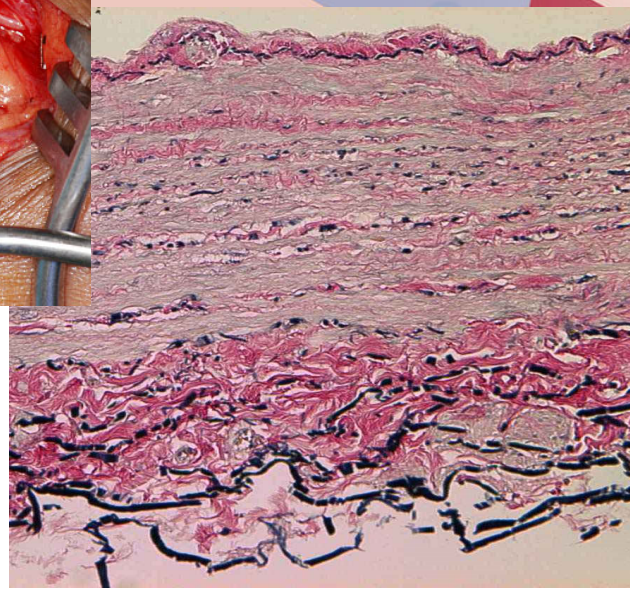
- Vonapanitase—cleaves elastin peptide bonds
- Single, local application (10 min) applied immediately after fistula creation
- Only active at site of application



Investigational Recombinant Human Elastase

- Vonapanitase—cleaves elastin peptide bonds
- Single, local application (10 min) applied immediately after fistula creation
- Only active at site of application
- Vonapanitase may stimulate outward vascular remodeling and inhibit intimal hyperplasia





Vonapanitase Fistula Trial Program

Study	Follow-up	N	Clinical Sites	Status
Phase 1	One year	66	10	Completed
Phase 2	One year	151	27	Completed
Phase 3 (PATENCY-1)	One year	311	31	Completed
Phase 3 (PATENCY-2)	One year	603	39	Recently Completed
		1,131		

All studies multicenter, randomized, double-blind, placebo-controlled
Four fistula clinical trial publications

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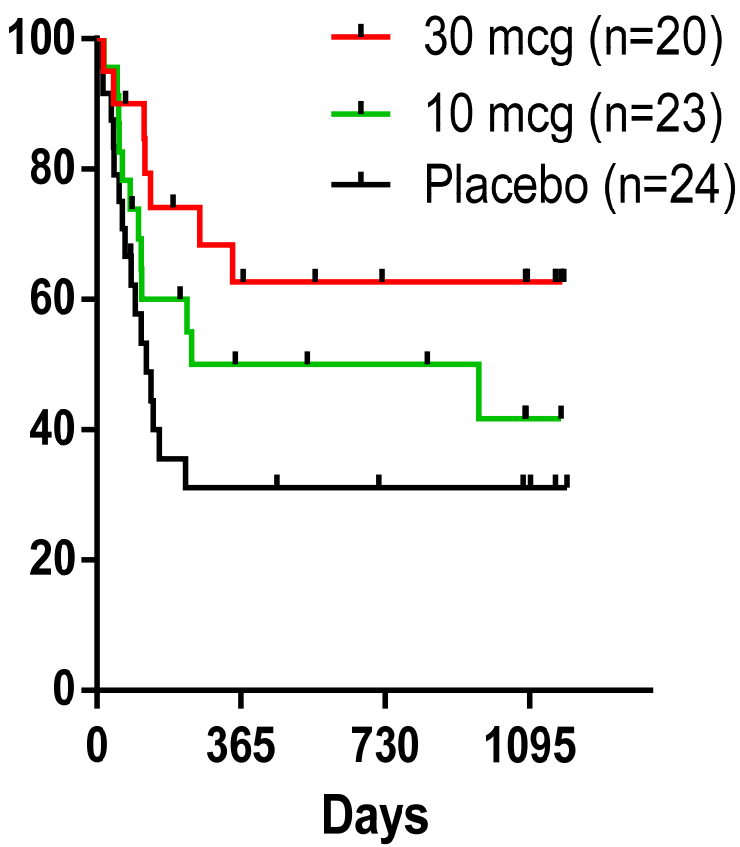

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- Patients (n~300) undergoing creation of radiocephalic fistulas (RCF)
- Randomized 2:1 to vonapanitase or placebo; Follow-up 1 year

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  - Primary – primary patency
  - Secondary – secondary patency
  - Tertiary – unassisted use for hemodialysis (HD), use for HD, maturation by ultrasound criteria, procedure rates

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- Endpoints
  - Primary – primary patency
  - Secondary – secondary patency
  - Tertiary – unassisted use for hemodialysis (HD), use for HD, maturation by ultrasound criteria, procedure rates
- Single primary, single secondary, and multiple tertiary and all endpoints were tested sequentially as pre-specified
  - An endpoint was tested at $p<0.05$ only if the preceding endpoint p-values were $p<0.05$, otherwise p-values were considered descriptive

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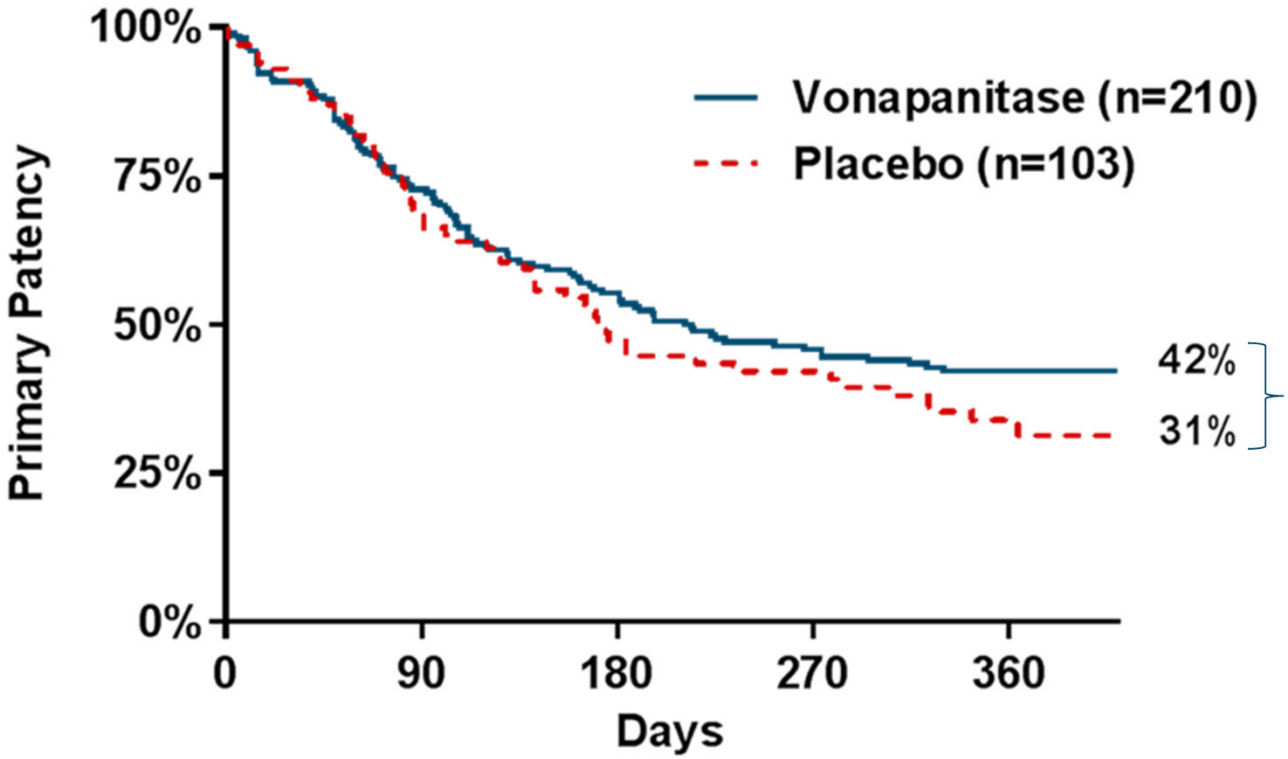
Primary Patency – Not Statistically Significant



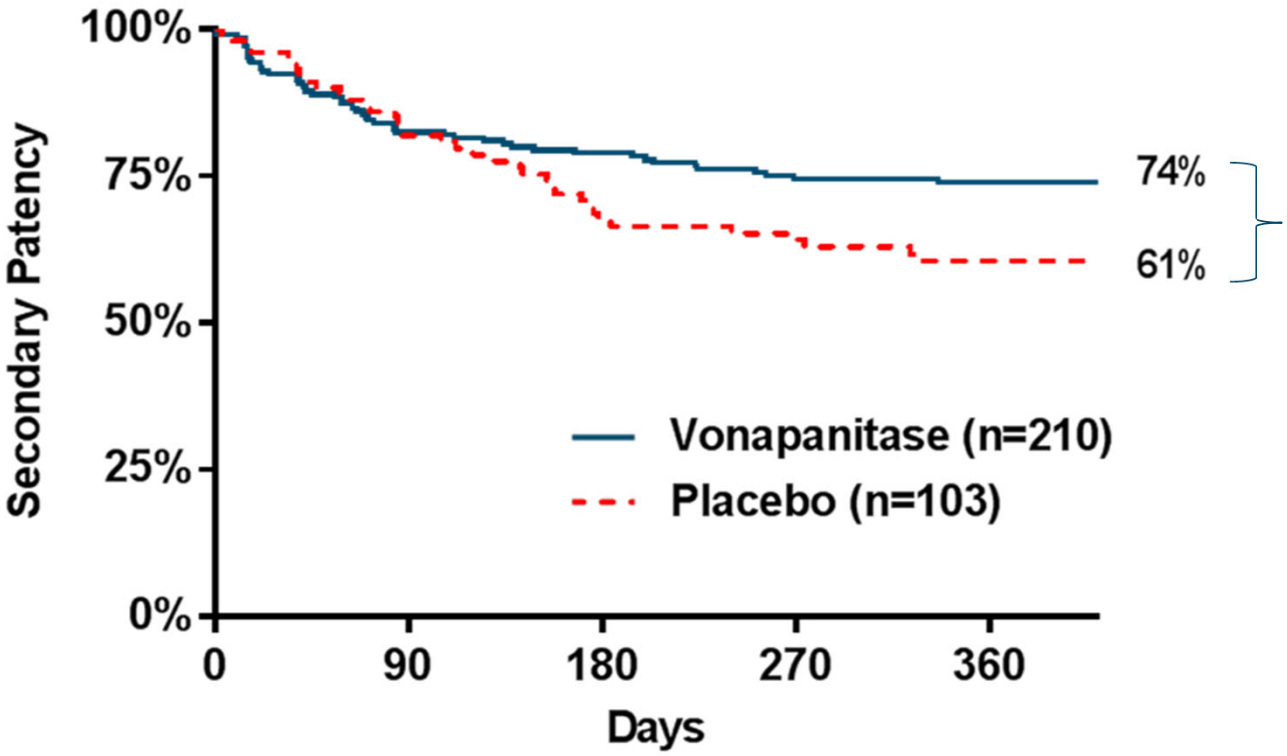
17% reduction in risk of primary patency loss (thrombosis or procedure to restore or maintain patency)
Hazard ratio 0.83,
95% CI 0.61 – 1.14, **p=0.254**

Numbers at risk for patency loss:

Vonapanitase	210	139	96	77	40
Placebo	103	66	37	32	19

PROTEON THERAPEUTICS

Secondary Patency



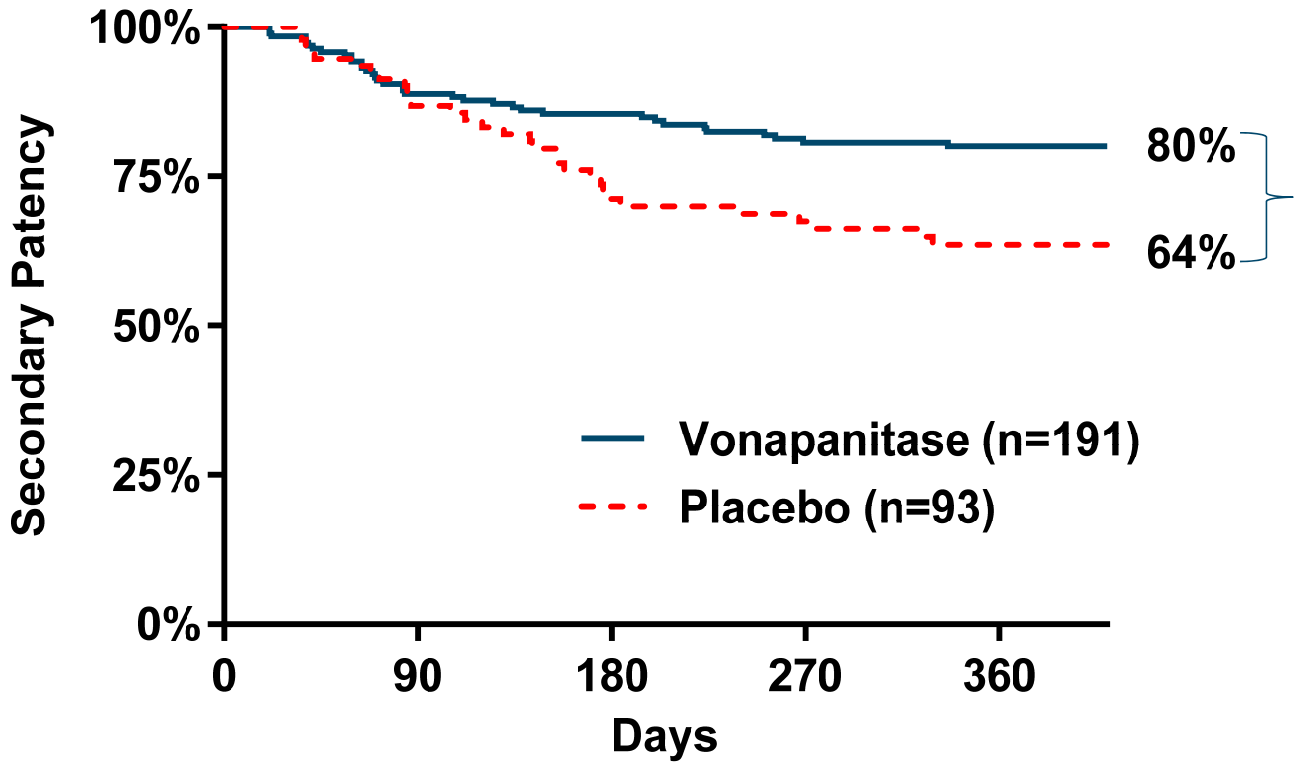
34% reduction in risk of secondary patency loss (abandonment)
Hazard ratio 0.66,
95% CI 0.43 – 1.00, **p=0.048**

Number at risk for patency loss:

Vonapanitase	210	163	147	135	82
Placebo	103	80	60	55	39

PROTEON THERAPEUTICS

Secondary Patency Excluding Early Failures



Number at risk for patency loss:

Vonapanitase	191	161	146	134	81
Placebo	93	78	58	53	37

48% reduction in risk of secondary patency loss (abandonment)
HR 0.52, 95% CI 0.32, 0.85, **p=0.007**

Pre-specified efficacy analysis that excludes 10% of placebo and 9% of vonapanitase patients with patency loss or early termination by Week 2 visit. Considered exploratory or sensitivity since the primary analysis population was ITT.

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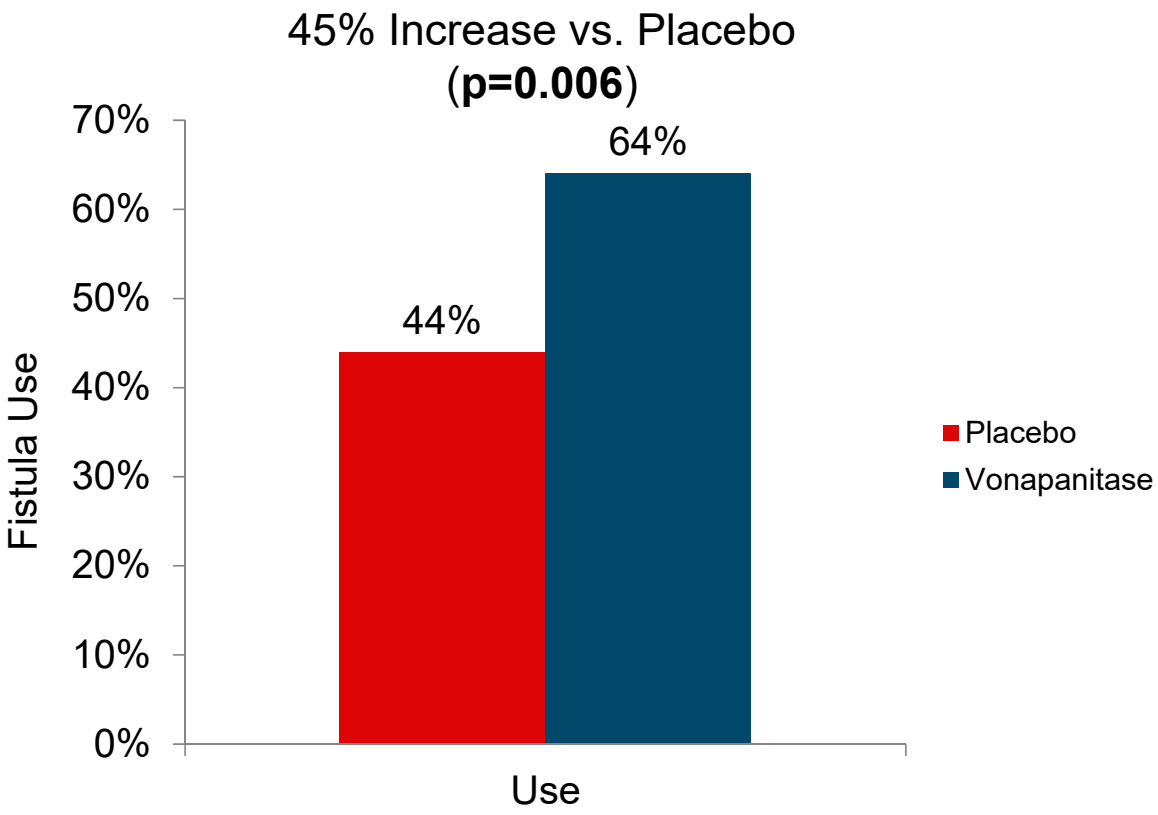
Use of the Fistula for Hemodialysis



Definition of fistula use

- Use of fistula for hemodialysis for ≥ 90 days
- For patients who did not initiate hemodialysis ≥ 90 days prior to last study visit, defined as ≥ 30 days of use including the last visit

This endpoint, arguably the most clinically meaningful, was not made primary since half the patients enrolled were pre-HD. Primary analysis population excludes patients who had indeterminate use (eg, never started HD).

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Vonapanitase Phase 3 Safety Profile

- No evidence of immunogenicity
- Adverse events consistent with underlying condition
- Adverse events comparable for vonapanitase and placebo

Adverse Events	Placebo (n=102)	Vonapanitase (n=209)
Vascular stenosis	40.2%	38.3%
Fistula thrombosis	26.5%	19.6%
Hypoaesthesia (numbness)	4.9%	5.3%
Procedural pain	5.9%	4.8%

Includes any adverse event that occurred in at least 5% of patients in either treatment group
Analysis excludes 2 patients who were randomized but not treated

PATENCY-2

- Nearly identical design but enrollment began a year later and was still enrolling at time results of PATENCY-1 became available

- Analysis plan allowed for a sample size adjustment based on the results of the PATENCY-1 trial

Changes to Protocol and Analysis Plan

- FDA agreed with validity of reordering endpoints to create new primary and secondary endpoints or co-primary endpoints
- Secondary patency and use for HD were made co-primary
- Sample size was increased to 600 to ensure adequate power

Patency-2 Baseline Characteristics

Age - years	57 ± 13
Weight - kg	96 ± 27
BMI – kg/m^2	32 ± 8
Male sex – n (%)	466 (76.0)
Race	
African American – n (%)	149 (24.3)
White – n (%)	418 (68.2)
Other – n (%)	46 (7.5)
Hispanic – n (%)	98 (16.0)
Tobacco usage	
Former – n (%)	263 (42.9)
Current – n (%)	83 (13.5)
Never – n (%)	267 (43.6)
Preexisting condition	
Diabetes – n (%)	404 (65.9)
Hypercholesterolemia – n (%)	440 (71.8)
Hypertension – n (%)	596 (97.2)
Congestive heart failure – n (%)	180 (29.4)
Ischemic heart disease – n (%)	171 (27.9)
Peripheral artery disease – n (%)	53 (8.6)
Cerebrovascular disease – n (%)	81 (13.2)
Chronic kidney disease	
Duration - months	58 ± 74
Diabetes primary cause – n (%)	285 (46.5)
HTN primary cause – n (%)	144 (23.5)
Other primary cause – n (%)	184 (30.0)
Prior renal transplant – n (%)	28 (4.6)
Hemodialysis (HD) history	
On HD at randomization – n (%)	278 (45.4)
Prior HD duration – months	9.5 ± 18.6
Current central catheter – n (%)	275 (44.9)
Prior permanent access – n (%)	54 (8.8)
Anesthesia	
General – n (%)	127 (21.1)
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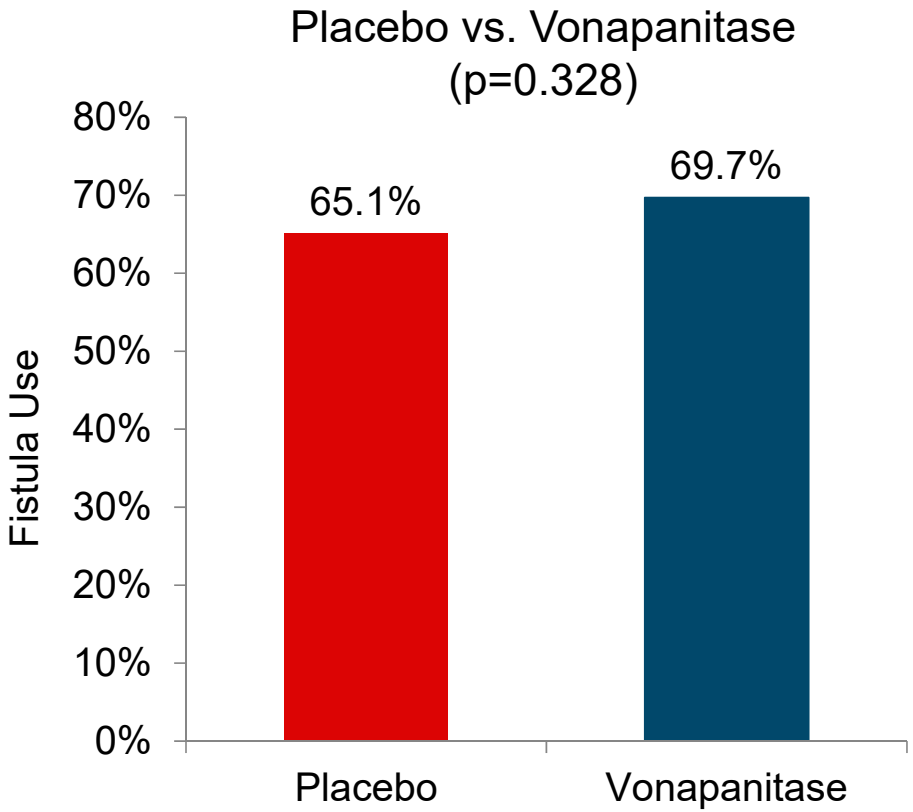
Co-Primary Endpoint: Fistula Use for Hemodialysis



- Defined as use of the fistula for two-needle hemodialysis for at least 90 days or, if hemodialysis was not initiated at least 90 days prior to the last study visit, for at least 30 days and including the patient's last study visit
- Results
  - No statistically significant difference between the arms (p=0.328)

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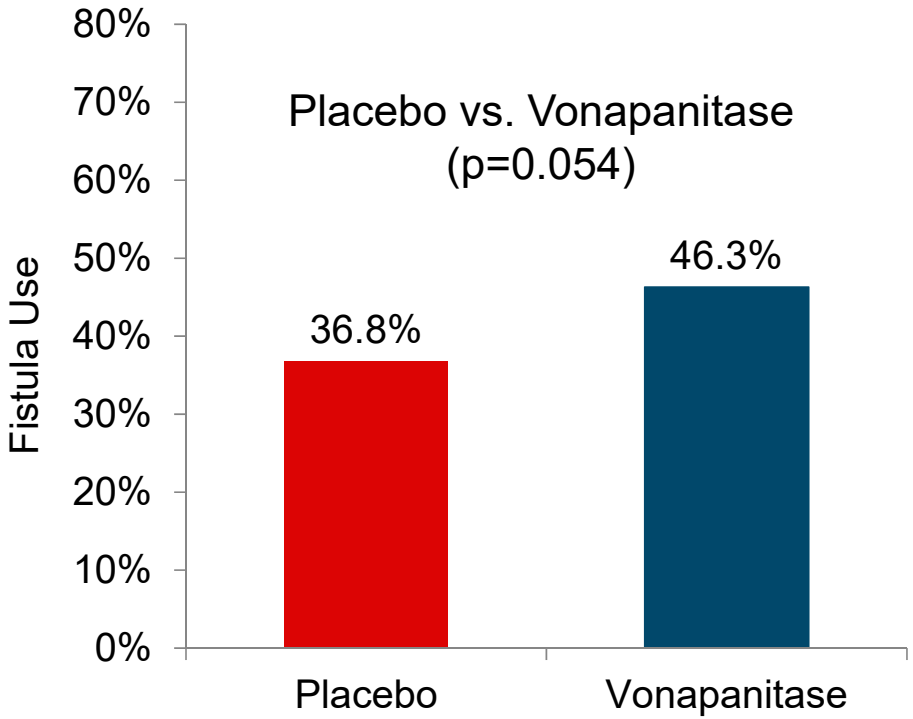
Unassisted Fistula Use for Hemodialysis



- Defined as before but required no primary unassisted patency loss prior to use (no prior corrective procedures or thrombosis)
- Results
  - No statistically significant difference between the arms (p=0.054)

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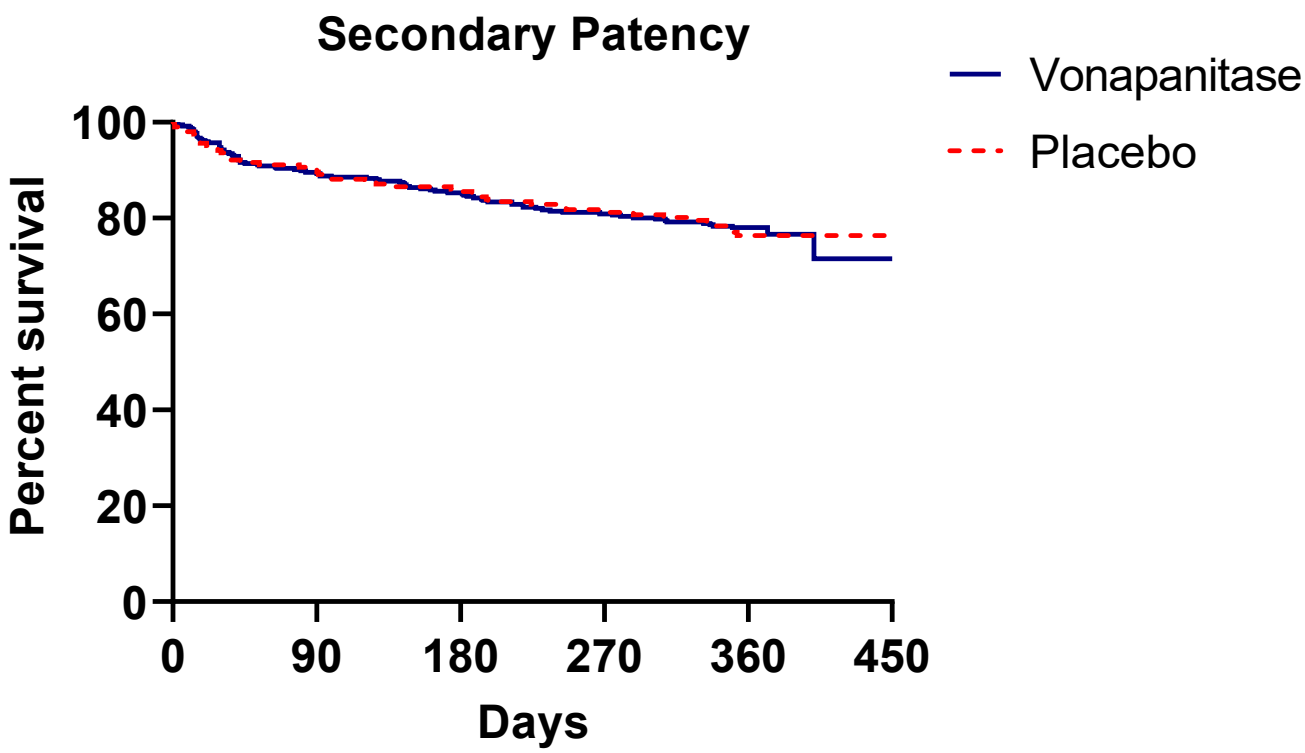
Co-Primary Endpoint: Secondary Patency



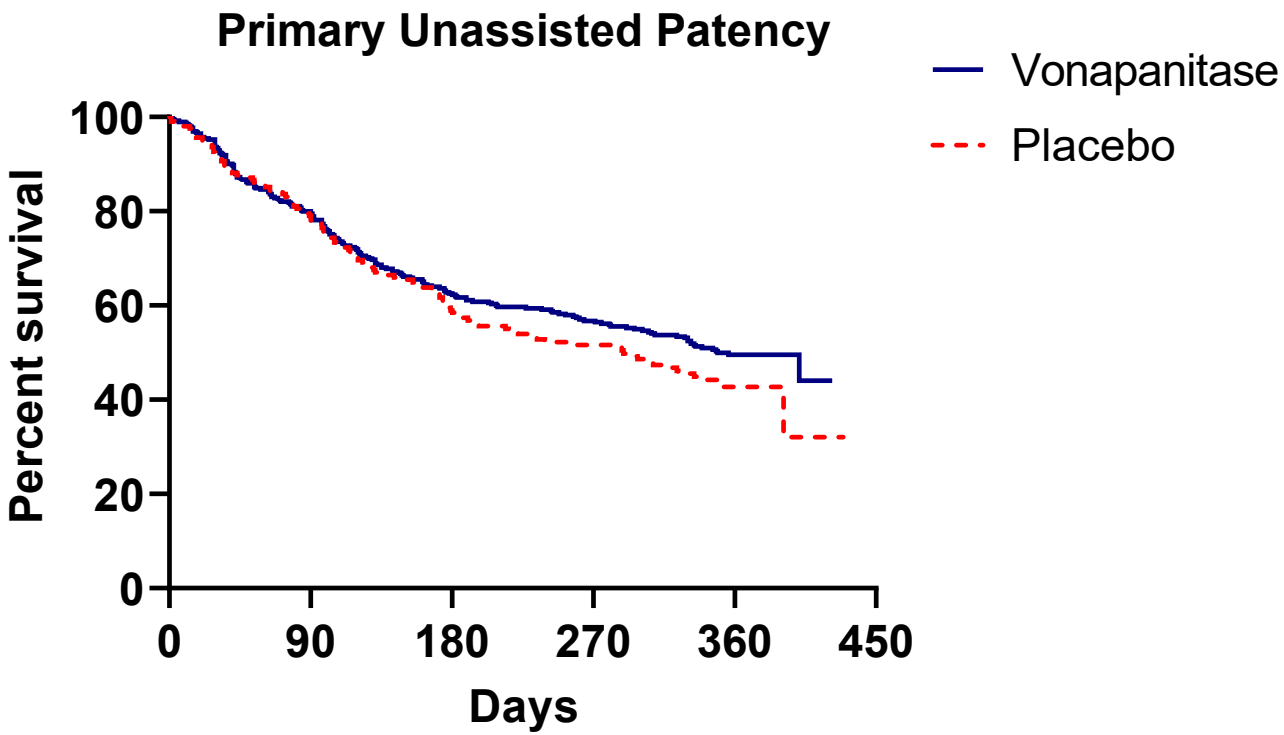
Defined as time from fistula creation to abandonment

Results

- No statistically significant difference between the arms (p=0.932)
- At one year, 78% and 76% of vonapanitase and placebo patients, respectively, retained secondary patency

PROTEON THERAPEUTICS

Other Endpoint: Primary Unassisted Patency



Defined as time from fistula creation to first occurrence of a fistula thrombosis or corrective procedure to restore or maintain patency

Results

- No statistically significant difference between the arms (p=0.178)
- At one year, 50% and 43% of vonapanitase and placebo patients, respectively, retained primary patency

PROTEON THERAPEUTICS

PATENCY-2 Safety Profile

- No evidence of immunogenicity
- Adverse events consistent with medical conditions experienced by kidney disease patients undergoing fistula surgery
- Adverse events comparable for vonapanitase and placebo

Adverse Events	Vonapanitase (n=399)	Placebo (n=204)
Vascular stenosis	35.1%	41.7%
Fistula thrombosis	16.8%	18.6%
Local swelling	5.0%	2.0%
Hematoma	5.0%	3.9%

Includes any adverse event that occurred in at least 5% of patients in either treatment group.

PROTEON THERAPEUTICS

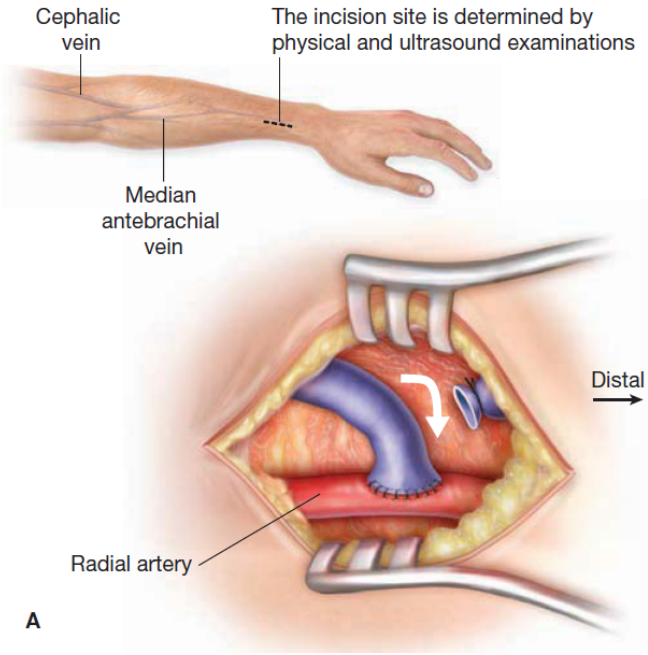
Additional Data Analyses Ongoing, to be Released Soon

- Use for hemodialysis - logistic regression
- Secondary patency - Cox modelling
- Maturation by ultrasound criteria
- Procedure rates
- Functional patency
- Serious adverse events
- Safety labs

PROTEON THERAPEUTICS

Summary

- Personally appreciative of the industry attention and investment in addressing this significant clinical problem in a complex patient population



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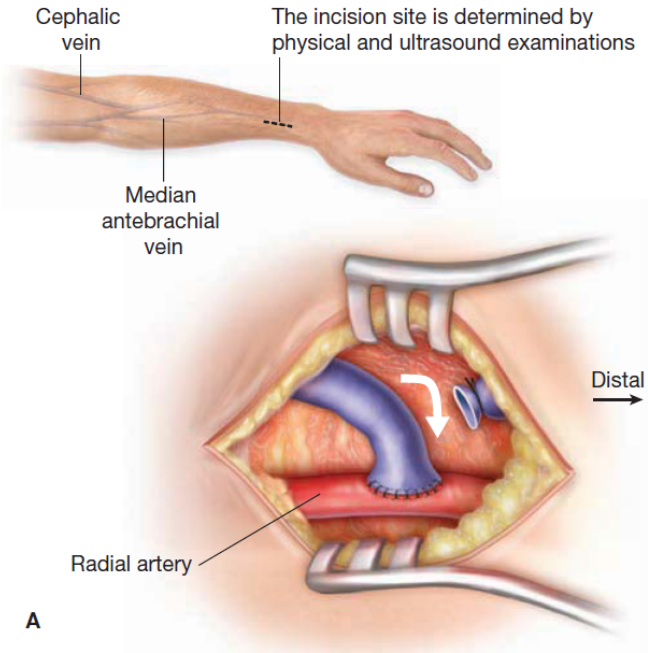
- Gratitude to the participating patients and their families



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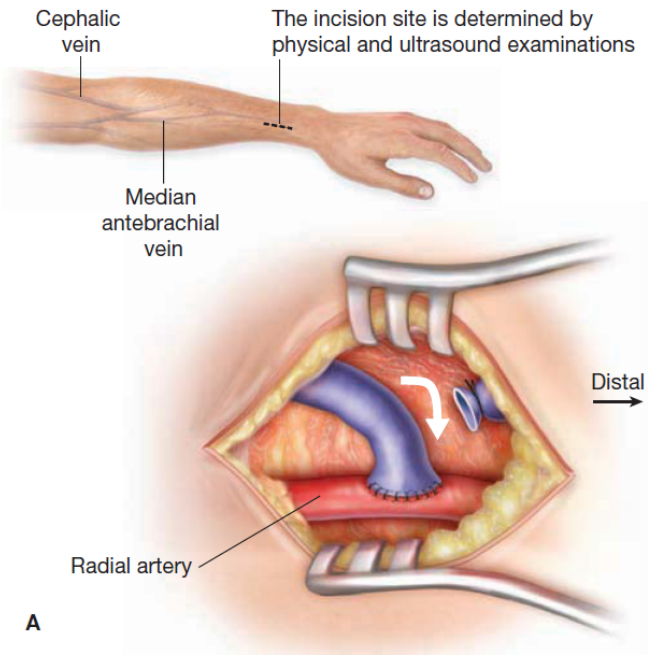
- Thank you to clinical trial sites



PATENCY-2 Clinical Sites

AKDHC Medical Research (Phoenix)	Knoxville Kidney Center	University of Alberta
AKDHC Medical Research (Tucson)	Lake Washington Vascular Center	University of Arizona
Baylor College of Medicine	Lehigh Valley Health Network	University of Chicago
Brigham and Women's Hospital	London Health Science Center (ON)	The University of Iowa Hospitals and Clinics
California Institute of Renal Research	Lutheran Hospital Network of Indiana	University of Louisville
Cardiothoracic and Vascular Surgeons (TX)	Maine Medical Center	University of North Carolina at Chapel Hill
Cleveland Clinic	McGill University Health Centre	University of Wisconsin School of Medicine
Faulkner Hospital	RenalCare Associates (IL)	VA Ann Arbor Healthcare System
Greenwood Leflore Hospital (MS)	Saint Luke's Hospital (MO)	VA Loma Linda Healthcare System
Henry Ford Hospital	Tulane University	VA Medical Center Long Beach
Houston Methodist Hospital	UMass Memorial Medical Center	VA Pittsburgh Healthcare System
Kaiser Permanente South San Francisco	Univ. Health Network Toronto General Hospital	Vancouver General Hospital
Kaiser Permanente Southern California	University of Alabama at Birmingham	Wake Forest Baptist Medical Center

Summary

- Personally appreciative of the industry attention and investment in addressing this significant clinical problem in a complex patient population
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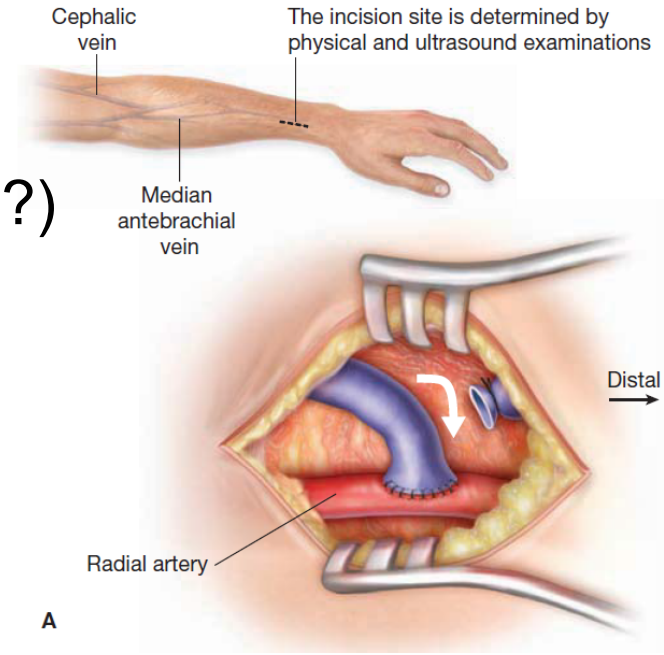
  (Did attentive, invested providers drive the substantial improvement in the placebo group?)



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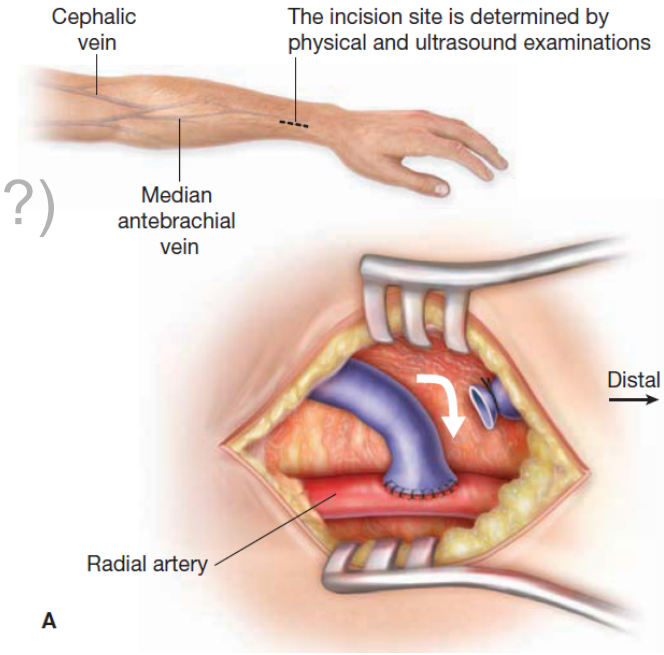

- Two negative Phase III Clinical Trials
- Vonapanitase unlikely to more forward as an adjunct to AVF maturation