PROTEON THERAPEUTICS™

February 2019

NASDAQ: PRTO

Cautionary Note Regarding Forward-Looking Statements

This presentation contains statements that are, or may be deemed to be, "forward-looking statements." In some cases these forward-looking statements can be identified by the use of forward-looking terminology, including the terms “believes,” “estimates,” “anticipates,” "expects," “plans,” "intends," “may,” “could,” “might,” “will,” “should,” “approximately,” “potential,” or, in each case, their negatives or other variations thereon or comparable terminology, although not all forward-looking statements contain these words. These statements, including our ability to fund operations into the first quarter of 2020, the number of patients to be enrolled in our ongoing and planned clinical trials, the timing of completing enrollment or releasing results for PATENCY-2, our interpretation of data from PATENCY-1 and other clinical and pre-clinical studies, the clinical and regulatory path forward for vonapanitase and whether additional studies will be necessary to support a Biologics License Application (BLA), whether and when we may submit a BLA or commercially launch in the United States, our ability to establish a commercially-ready supply chain, our intellectual property position, the significance or clinical utility of any approved product, the market opportunity, standard of care and reimbursement for improving fistula outcomes, and those relating to future events or our future financial performance or condition, business strategy, current and prospective product candidates, planned clinical trials and preclinical activities, product approvals, research and development costs, current and prospective collaborations, timing and likelihood of success, plans and objectives of management for future operations, and future results of anticipated product candidates, involve substantial known and unknown risks, uncertainties and other important factors that may cause our actual results, levels of activity, performance or achievements to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties and other factors, including whether our cash resources will be sufficient to fund the our operating expenses and capital expenditure requirements for the period anticipated; whether data from early clinical trials will be indicative of the data that will be obtained from future clinical trials; whether vonapanitase will advance through the clinical trial process on the anticipated timeline and warrant submission for regulatory approval; whether such a submission would receive approval from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies on a timely basis or at all; and whether we can successfully commercialize and market our product candidates, are described more fully in our Annual Report on Form 10-K for the year ended December 31, 2017, as filed with the Securities and Exchange Commission (“SEC”) on March 14, 2018, and our subsequent Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, as filed with the SEC, particularly in the sections titled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations." In light of the significant uncertainties in our forward-looking statements, you should not place undue reliance on these statements or regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. The forward-looking statements contained in this presentation represent our estimates and assumptions only as of the date of this presentation and, except as required by law, we undertake no obligation to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise after the date of this presentation.

This presentation also contains estimates, projections and other information concerning our industry, our business, and the markets for our drug candidates, as well as data regarding market research, estimates and forecasts prepared by our management. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties.

Clear Path Forward for Potentially Transformative Treatment for CKD Patients

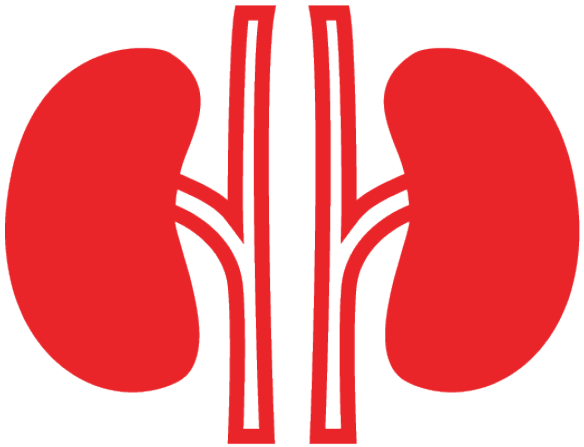
- Results from PATENCY-1 (first Phase 3 trial) supported Breakthrough Therapy Designation
  - FDA's criteria for BTD: potential treatment for serious or life-threatening condition and **preliminary clinical evidence indicates drug may offer substantial improvement (clear advantage) over available therapies on one or more clinically significant endpoints**
  - PATENCY-1 showed improvement in pre-specified endpoints of use for HD (p=0.006) and secondary patency (p=0.048); primary endpoint not statistically significant
  - Adverse events comparable for vonapanitase and placebo
- FDA agreement on filing strategy with co-primary endpoints in PATENCY-2
  - Endpoint definitions same as PATENCY-1
  - If each successful at $p \leq 0.05$, BLA can be filed without additional trials; PATENCY-1 would be considered supportive
  - Data expected March 2019; BLA filing expected in 2019 and MAA filing expected in 2020
  - BTD, fast track and orphan designations for hemodialysis vascular access
- Significant unmet medical need to improve radiocephalic fistula outcomes
  - Reduce catheter exposure, the worst form of access, associated with increased risk of sepsis, thrombosis, hospitalization and mortality
  - If successful, vonapanitase would represent the most significant innovation in vascular access in decades
- Improving radiocephalic fistula outcomes is a $1 billion market opportunity in the US

Experienced Management Team

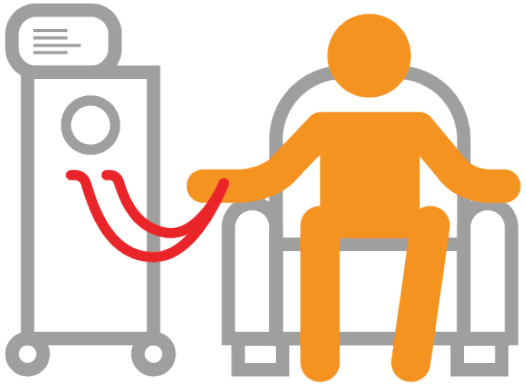
	Position	Prior Experience
Timothy Noyes	President and CEO	Genzyme Renal (President), GelTex Pharmaceuticals (President) Merck & Co.
Steven Burke, M.D.	SVP and CMO	Genzyme (SVP, Medical & Regulatory Affairs,) GelTex Pharmaceuticals (VP Clinical Research), Glaxo
George Eldridge	SVP and CFO	Targanta Therapeutics (CFO), Therion Biologics, Curis, Kidder Peabody
Scott Toner	SVP, Marketing	OPKO Health's Renal Division (VP US Marketing & Sales), Reata Pharmaceuticals, AMAG Pharmaceuticals, Abbott Laboratories
Daniel Gottlieb	Vice President, Corporate Development	Abbott Vascular (Strategic Marketing) Guidant (Corporate Venture Capital and Business Development)
Pam Gustafson	Vice President, Clinical Research	Trine Pharmaceuticals (Director of Clinical Operations) AAI International
Brad Hartman	Vice President, People	Unum Therapeutics (VP, People), ConnectedSearch, Vertex and Dyax
Matthew Kowalsky	Vice President, Legal	Sanofi Genzyme (Senior Corporate Counsel), Cubist, Lantheus Medical
John Najim	Vice President, Manufacturing	Dyax Corp. (Associate Director of Manufacturing) GTC Biotherapeutics (Process Development Manager)

Fistula Background

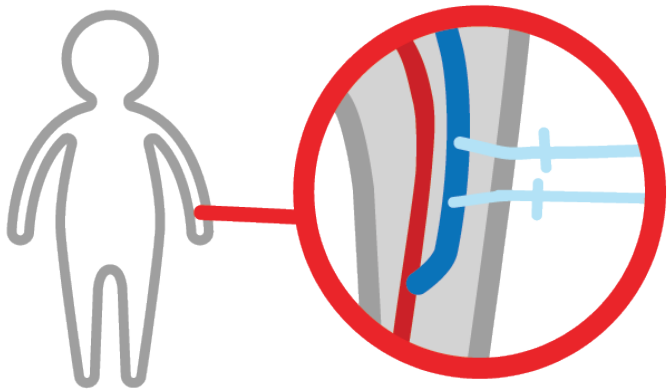
Vascular Access: A Hemodialysis Patient's Lifeline



Healthy kidneys remove waste and excess fluid continuously, 24 hours per day



Patients with kidney failure typically undergo hemodialysis three times per week (3-4 hours/session)



Hemodialysis requires a high flow vascular access, preferably an arteriovenous fistula

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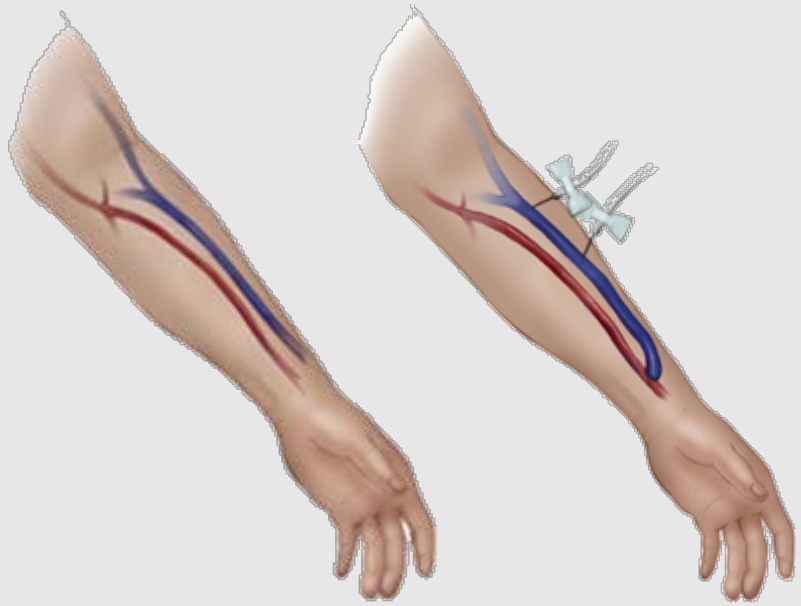
Radiocephalic (Forearm) Fistula Is Preferred Form of Vascular Access

- Fistulas used by 2/3 of US hemodialysis patients
  - Lowest rates of infection, thrombosis, intervention and related hospitalization
  - Lowest cost of care
- Recommended by key stakeholders
  - National Kidney Foundation (NKF) KDOQI Guidelines
  - CMS' Fistula First/Catheter Last Initiative
- Radiocephalic (forearm) fistula optimal
  - Reduced risk of hand ischemia (steal syndrome), central stenosis and heart failure
  - Preserves additional access sites in arm if needed

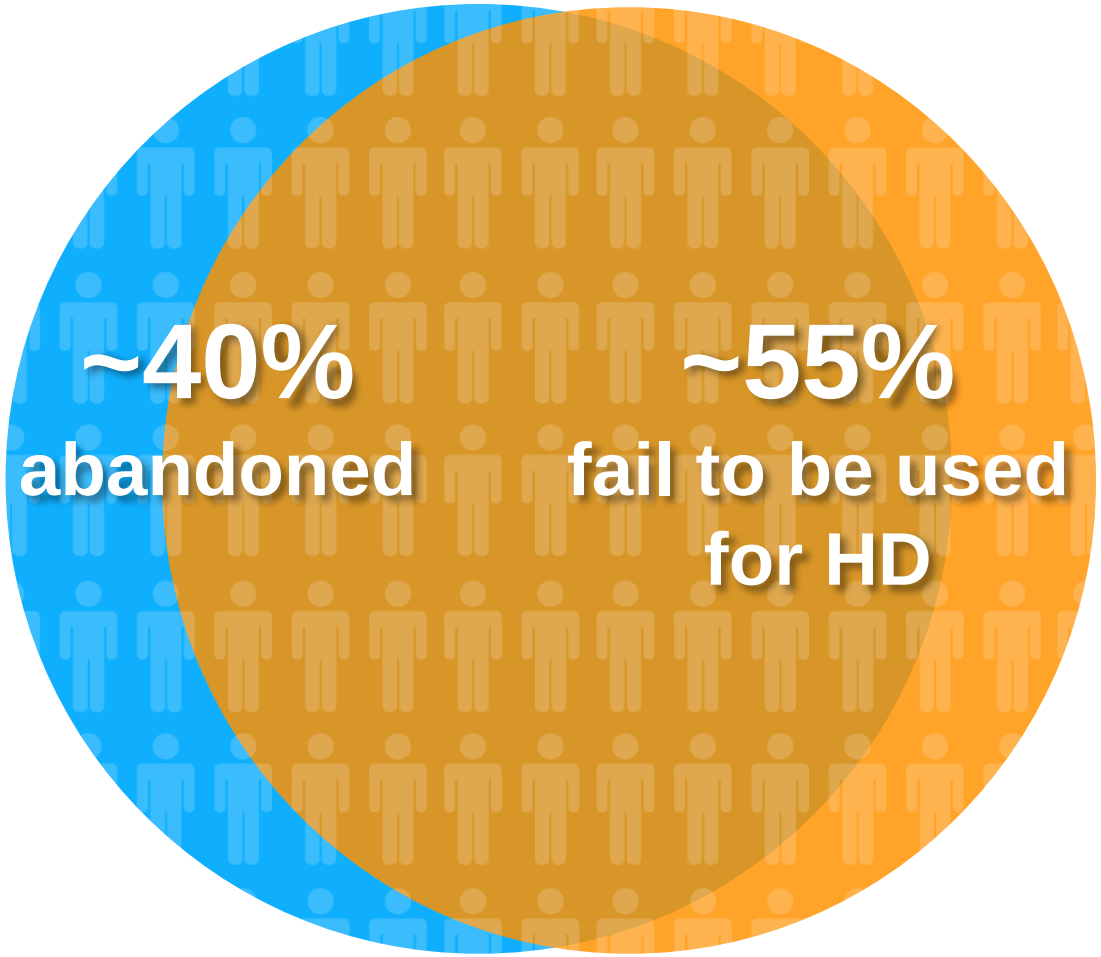
Radiocephalic Fistula

Preferred Form of Access



- Surgical connection of artery and vein
- To become usable, vein must remodel, increase in blood flow and diameter (~3 month process)

Gold Standard Radiocephalic Fistula Frequently Fail in First Year, With Grave Consequences



- Patient must dialyze with a catheter
- New access surgery for possible upper arm fistula or graft
- Risk of exhausting all access sites in arms

"The use of hemodialysis catheters is associated with poor quality of life, increased risk of sepsis, stenosis and thrombosis, low blood flow rates, and increased hospitalizations and mortality." [1]

Failure data from PATENCY-1. [1]Chaudhry 2011.

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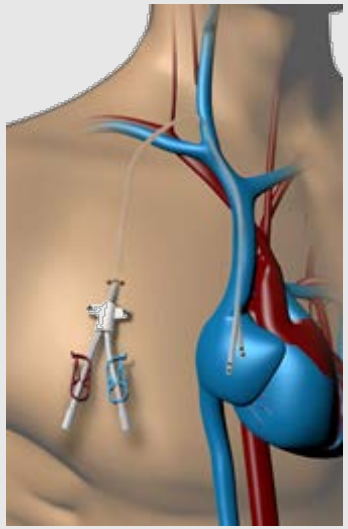
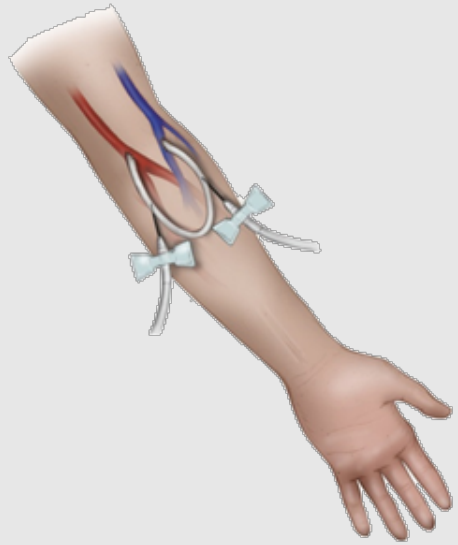
Fistula Failure Often Results in Patient Reliance on Less Desirable Forms of Vascular Access

Catheter
Least Desirable



- Required when fistula or graft is not yet usable or is abandoned
- Highest rates of infection, hospitalization and mortality
- ~80% start dialysis on a catheter
- ~15% use long term

Arteriovenous Graft
For Patients Unsuitable for Fistula



- For patients experiencing fistula failure or lacking suitable vessels
- Higher rates of failure, interventions and infection compared to fistulas
- ~20% use long term

US figures

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Clinical Implications of Catheter Use Are Severe

Annual relative risk of mortality 1.40–2.74[1]

Reduced dialysis adequacy (patients with Kt/V < 1.20: 25% for catheter vs. 10% for fistula/graft)[2]

8x rate of bloodstream infections[3]

Reduced quality of life[4]

Initiate HD on a catheter

- 2x mortality risk in first year[5]
- 3x mortality risk in first three months (overall 47/100 py)[6]
- 2x rate hospitalization in first six months (1.9 vs. 0.9 ppy)[7]
- 3x rate hospitalization for infection in first year (21% vs. 7%)[8]

Fistula fails to be used

- 2x rate catheter infections in first year (2.2 vs. 1.0/year)[9]
- 4x rate sepsis hospitalizations in first year (1.4 vs 0.3/year)[9]

Fistula/graft abandoned

- 2x mortality risk for up to one year[5,10]
- 3x infection-related mortality risk for one year[10]
- 22% increase in risk of hospitalization for one year[11]

Relative risks compared to fistulas or fistulas/grafts. [1]Vassalotti 2012. [2]Lee 2005. [3]Nguyen 2017 (2.16 vs. 0.26 per 100-patient months) [4]Wasse 2007. [5]Lacson 2009. [6]Lukowsky 2012. [7]Ng 2011. [8]Kazakova 2016 (septicemia or bacteremia). [9]Al-Balas 2016. [10]Allon 2006. [11]Lacson2010.

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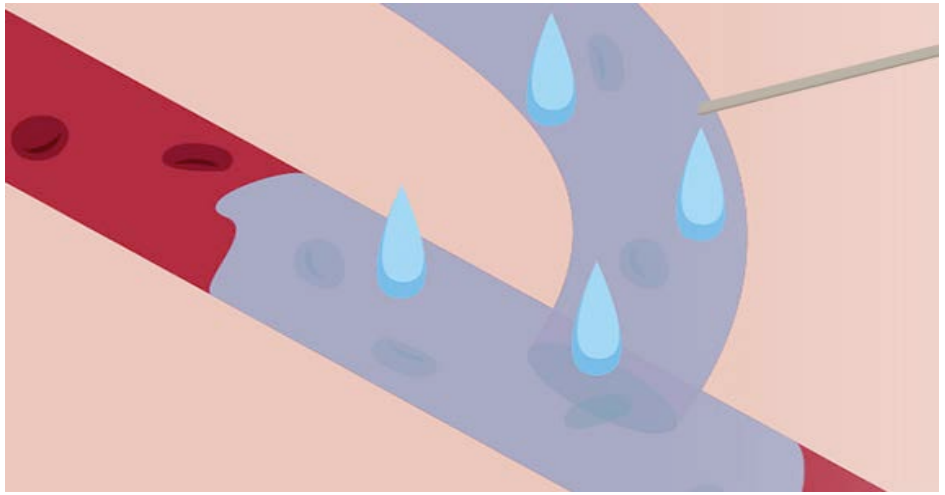
Vonapanitase

Vonapanitase Overview

- Investigational recombinant human elastase
- 25 kilodalton serine protease that cleaves peptide bonds in the protein elastin
- Elastin is the principal component of elastic fibers in blood vessels that impart elasticity
- Single, local application (10 minutes) to the external surface of the fistula immediately after creation
- Active at site of application with no systemic effects observed since inactivated by blood
- Decades of research demonstrate key role of elastin degradation in vascular remodeling



Two Primary Causes of Fistula Failure

Insufficient Outward Vascular Remodeling

- Outward remodeling necessary for successful fistula maturation
  - Structural changes in the vessel wall, resulting in an increase in diameter and flow[1-3]
  - Involves proliferation of cells (myofibroblasts) in the vessel wall[1]
  - MMPs (endogenous elastases) fragment elastin fibers in the vessel wall, critical to this process[1,2]
- Vessel injury inhibits MMP activity, resulting in insufficient remodeling

Neointimal Hyperplasia

- Vessel injury results in platelet aggregation and release of chemo-attractant factors in the vessel lumen[1,4]
  - Proliferation of cells (myofibroblasts) in the vessel wall
  - Cell migration to the vessel lumen
- Results in formation of a stenosis or thrombosis in the vessel lumen, limiting blood flow[1,2,4]

Enhancing outward remodeling and inhibiting neointimal hyperplasia may improve fistula use and prolong fistula survival

MMPs: matrix metalloproteinases. [1]Hu Sem Vasc Surg 2016, [2]Dixon KI 2006, [3]Robbin Radiology 2002, [4]Roy-Chaudhury JASN 2006.

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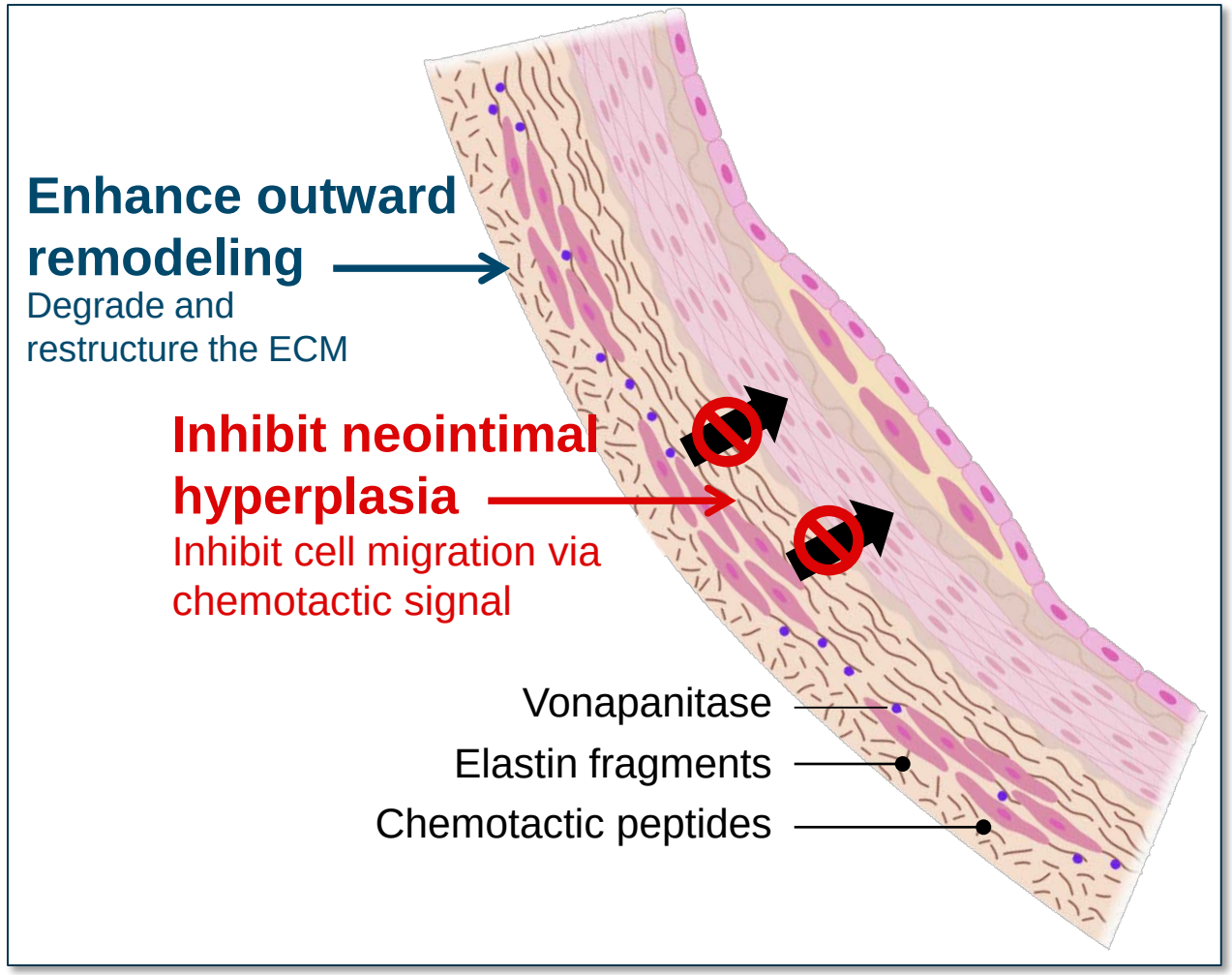
Vonapanitase, an Exogenous Elastase, Partially Fragments Elastin Fibers in the Adventitia

- May enhance outward remodeling
  - Elastin fragmentation via endogenous elastase is an early and essential step in remodeling[1,2]
  - Process often inhibited following fistula creation[3]
  - Vonapanitase augments elastin fragmentation[4]
  - Stimulates cell proliferation and degradation and restructuring of the extracellular matrix (ECM), enabling increases in diameter and blood flow[5]
- May inhibit neointimal hyperplasia
  - Cells migrate to the vessel lumen following vessel injury, resulting in stenosis formation[5,6]
  - Elastin fragmentation generates peptides in the adventitia that are chemotactic to these cells[7,8]
  - Chemotactic signal inhibits cell migration to the lumen, reducing stenosis formation[9,10]



[1]Dixon KI 2006, [2]Tronc 2000, [3]Sho 2002, [4]Wong 2016, [5]Hu Sem Vasc Surg 2016, [6]Roy-Chaudhury JASN 2006, [7]Senior 1984, [8]Ooyama 1994, [9]Amabile 2002, [10]Wong 2002.

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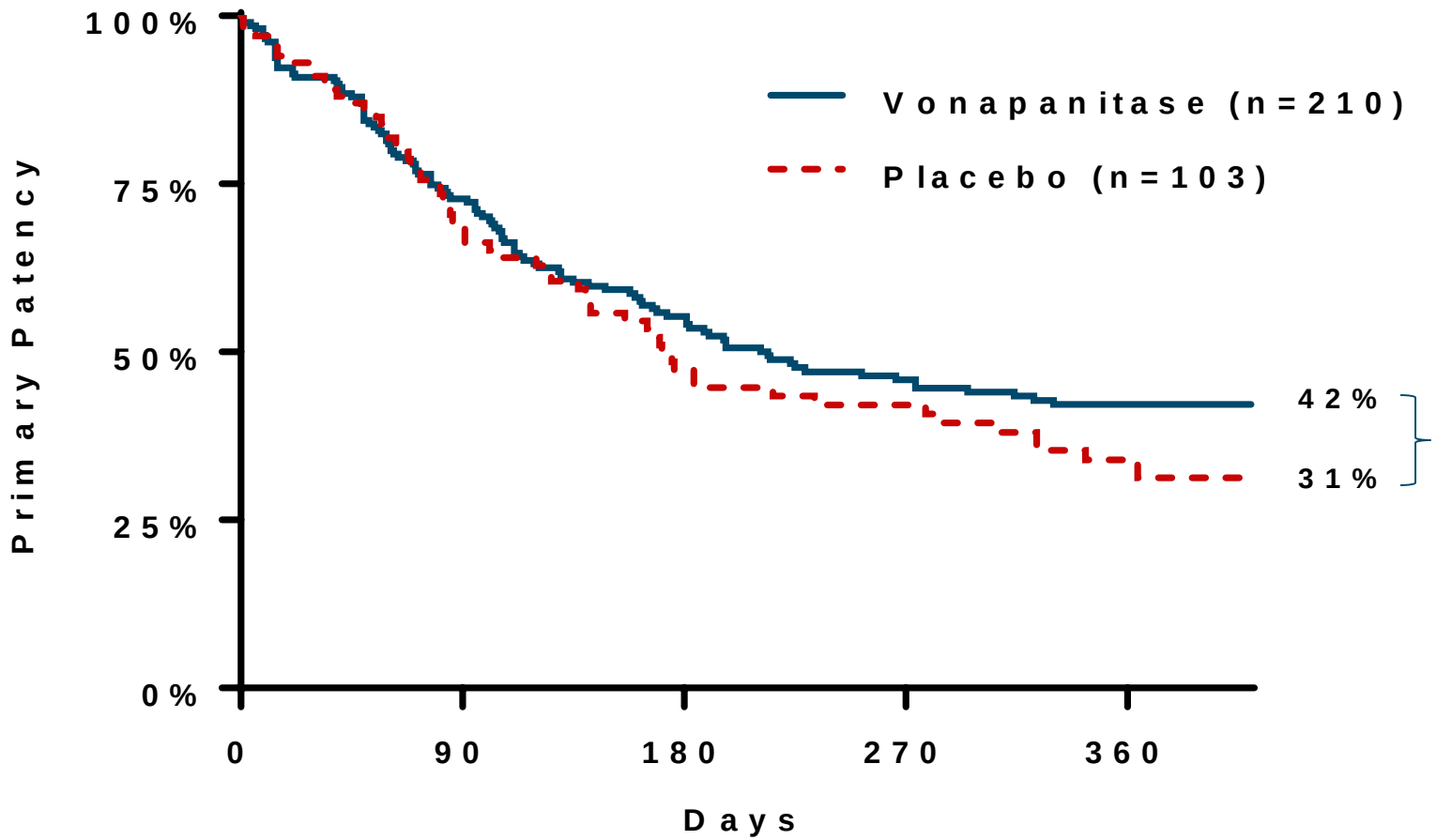
Phase 3 PATENCY-1 Trial

Design	Multicenter, randomized, double-blind, placebo-controlled
N	313 patients in U.S.
Patients	Patients with CKD on or expecting to initiate hemodialysis and undergoing surgical creation of a radiocephalic fistula
Dose	Vonapanitase 30 mcg vs. placebo (2:1 randomization)
Primary Endpoint	Primary unassisted patency (time from fistula surgical creation until first thrombosis or procedure to restore or maintain patency)
Secondary Endpoint	Secondary patency (time from fistula surgical creation until fistula abandonment)
Tertiary Endpoints	Use for hemodialysis Fistula maturation by ultrasound criteria Rate of procedures

Vonapanitase Increased Primary Unassisted Patency – Not Statistically Significant



17% reduction in risk of primary unassisted 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

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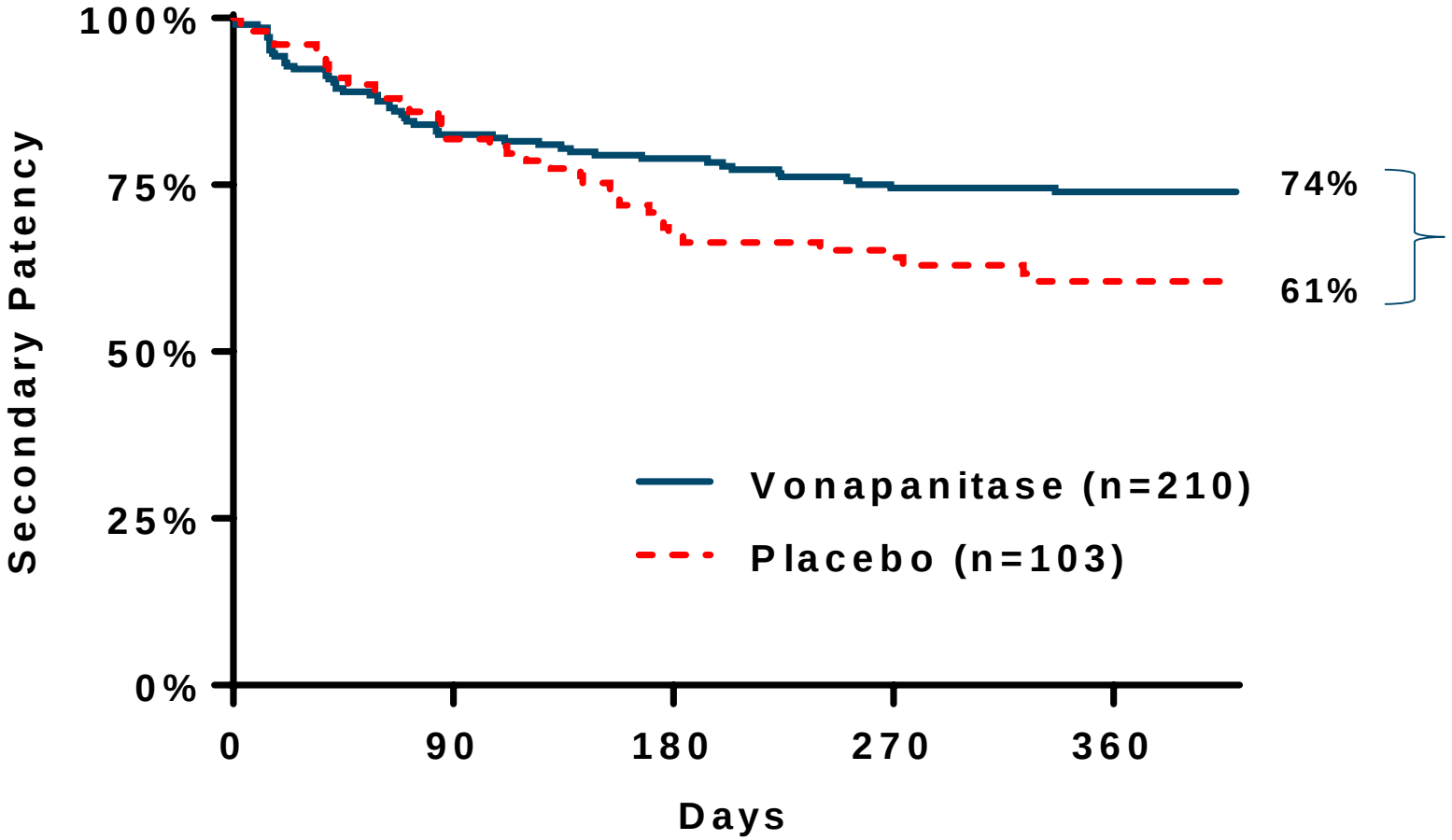
Vonapanitase Increased Secondary Patency



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

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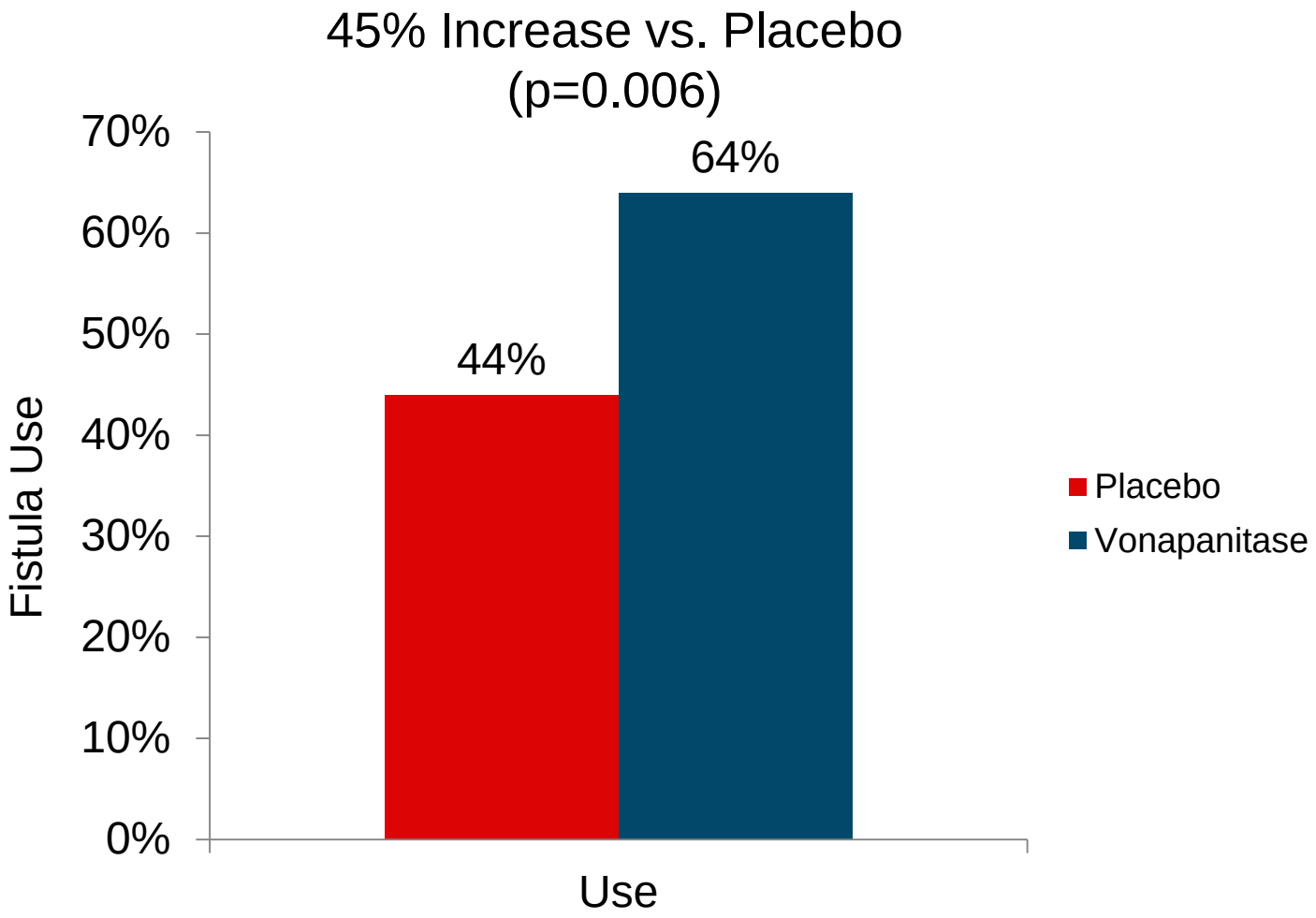
Vonapanitase Increased Use of the Fistula for Hemodialysis



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

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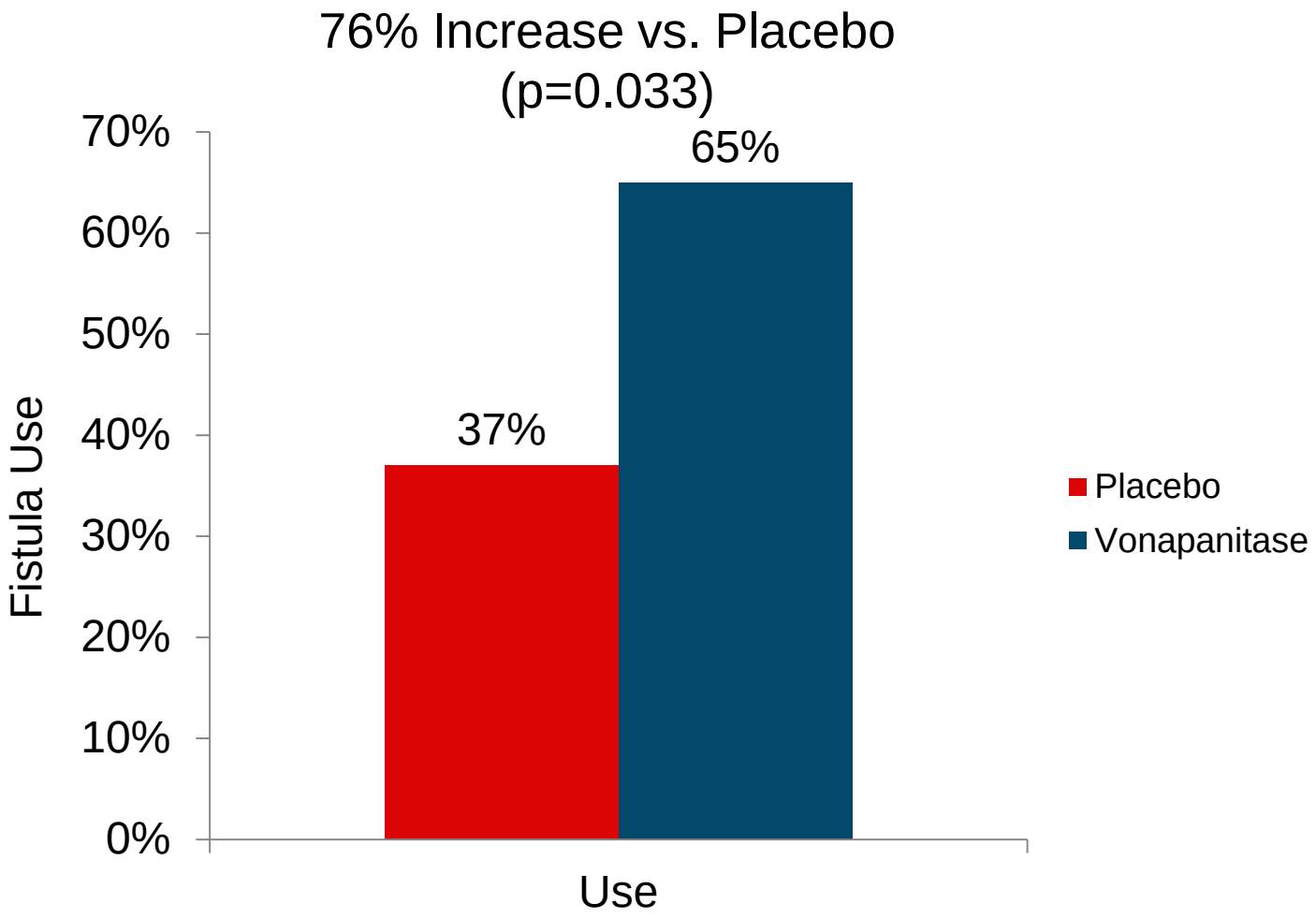
Vonapanitase Increased Use of the Fistula for Hemodialysis – At HD Initiation



- Evaluated in patients predialysis at study initiation who progressed to HD during the study (excludes patients who remained predialysis during the study).
- Analysis includes patients who had their fistula created at least 6 weeks prior to HD initiation.

Post hoc analysis. Fistula use defined utilizing the same definition as the tertiary endpoint. N=68.

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Vonapanitase Phase 3 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	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

Summary of PATENCY-1 Results

- Pre-specified endpoints demonstrated a positive drug effect
- Improvements observed in clinically important endpoints
  - Use for hemodialysis (p=0.006)
  - Secondary patency (p=0.048)
- Adverse events comparable for vonapanitase and placebo
- Implications of PATENCY-1
  - Results support PATENCY-2 co-primary endpoints
  - FDA agreed that PATENCY-2 can serve as pivotal study
  - FDA granted Breakthrough Therapy Designation

Address key clinical questions for physicians and patients

1. Was the fistula successfully used for hemodialysis?
2. How long did the fistula survive?

"…clinical evidence indicates drug may demonstrate substantial improvement…such as substantial treatment effects in clinical development"

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Ongoing Phase 3 PATENCY-2 Trial

Design	Multicenter, randomized, double-blind, placebo-controlled
N	603 treated patients in U.S. and Canada
Patients	Patients with CKD on or expecting to initiate hemodialysis and undergoing surgical creation of a radiocephalic fistula
Dose	Vonapanitase 30 mcg vs. placebo (2:1 randomization)
Co-Primary Endpoints	Secondary patency (time from fistula surgical creation until fistula abandonment) Fistula use for hemodialysis
Other Efficacy Endpoints	Primary unassisted patency Procedure rate Fistula maturation

Endpoint definitions same as PATENCY-1

PATENCY-2 Powered Based on PATENCY-1 Results

Secondary Patency

- 88% power for p≤0.05 if observed improvement in PATENCY-1 is true (61% to 74%)
- Based on simulations, expected p-value < 0.01 if PATENCY-1 results observed

Use for Hemodialysis

- 98% power for p≤0.05 if observed improvement in PATENCY-1 is true (44% to 64%)
- Based on simulations, expected p-value < 0.001 if PATENCY-1 results observed

Endpoints were closely related in PATENCY-1: of the fistulas that were not used for hemodialysis, 92% were abandoned

Improving Radiocephalic Fistula Outcomes Is a $1 Billion Market Opportunity in the US

- 130,000 fistulas created annually (~35%-40% radiocephalic)
  - Driven by >100,000 new hemodialysis patients per year
- Expect attractive coverage and reimbursement environment
  - Primarily Medicare outpatient ➔ Part B reimbursement
  - Excluded from ESRD payment bundle
- Market research indicates vonapanitase likely to become standard of care
  - Clear understanding of medical need by all stakeholders
  - Surgeons are eager to improve results and receptive to innovation
  - No competitive therapies available; few in development
- Fistulas that are not used for HD cost Medicare > $21,000 in incremental costs in Year 1 and > $10,000 in each of Years 2 and 3 following creation

Analysis of 3901 Medicare patients who initiated dialysis with a catheter and underwent subsequent fistula creation. Per patient per year figure.

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Strong IP Estate

Family	Description	Status / Commentary
1	• Uses of elastases for increasing diameter of biological conduits (including arteries and veins) and reduction of intimal hyperplasia or stenosis. • Uses of elastases to treat vascular access sites to prolong hemodialysis access	• First nonprovisional filing in 2000 • Patents issued in US, EP, CA, JP and HK
2	• Use of elastases for compliance matching at vascular anastomoses	• First nonprovisional filing in 2004 • Patents issued in US, JP and AU
4	• Low trypsin and trypsin-free compositions of mature human type I elastases, and related therapeutic uses • Methods of manufacturing mature elastases • Engineered pro-elastase proteins and related DNA molecules and host cells	• First nonprovisional filing in 2008 • Patents issued in US, EP, JP, AU, NZ, MX, IL, IN, CN, AU, KR, RU, TW and HK and pending in CA, AR and BR • Project patent term extension into 2033 in US and EU

Patent protection into 2030 in US; through 2028 in EU
(2033 US/EU with expected extensions)

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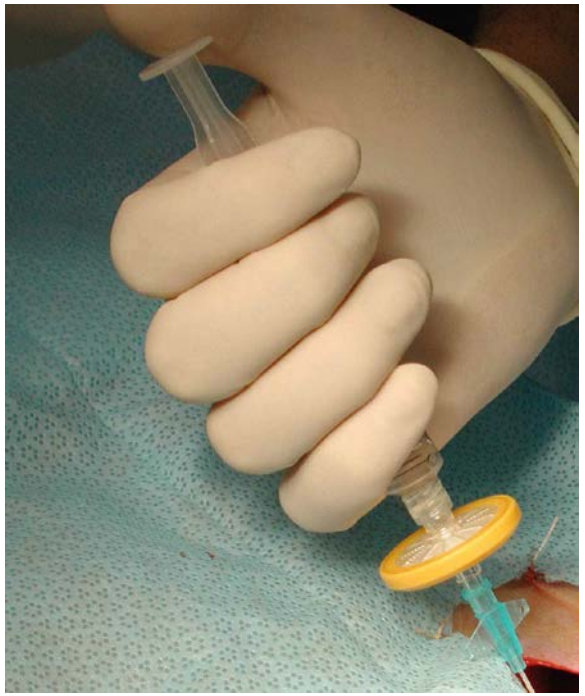
Vonapanitase for Peripheral Artery Disease (PAD)

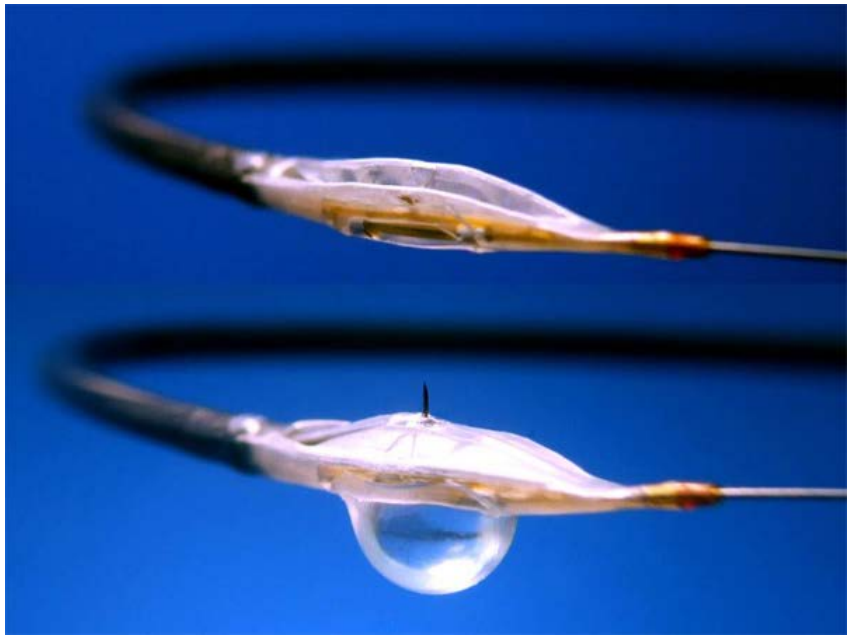
- Compelling near-term follow-on clinical area after fistulas
  - Significant unmet medical needs globally
  - Strategic fit with vascular access program (physician, patient, site of service)
- Nonclinical program evaluated safety and biologic effect
  - Vonapanitase treatment dilated diseased tibial arteries ex vivo
  - Potential therapy as complement to angioplasty or alone (“monotherapy”)
- Completed a successful Phase 1 study
  - Encouraging safety and technical feasibility of treatment via drug delivery catheter
- Conducting an additional Phase 1 study in clinical area not addressed by current therapies
  - Vonapanitase as adjunct to angioplasty below the knee

Potential PAD Applications



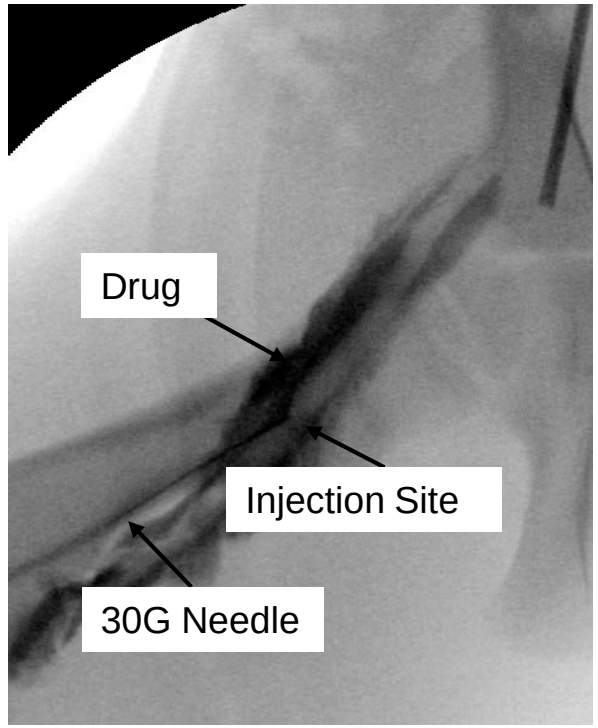
Surgical

- Patients undergoing peripheral bypass
- Similar concept to Phase 3 fistula program



Endovascular

- Active Phase 1 study in patients undergoing angioplasty of an artery below the knee
- Builds on prior Phase 1 PAD study



Percutaneous

- Active Phase 1 study (not enrolling) in patients with disease of the superficial femoral artery
- Possible alternative to angioplasty; delivery via needle

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Drug Supply Chain

- Drug substance
  - Manufactured at Lonza in Switzerland; one batch generates >1 million fistula doses
  - Current cGMP stability at >5 years at -80°C; cGMP testing performed at PPD
    - Drug substance process validation campaign completed
- Drug product
  - Manufacturing at Jubilant Hollister-Stier in U.S.
  - Current cGMP stability at 2 years at 2-8°C (refrigerated); cGMP testing performed at PPD
    - Drug product validation studies (2018)
- Intend to use a third-party logistics provider for commercial drug distribution, storage, etc.

Strong Financial Position

- $26.2 million of cash, cash equivalents and marketable securities at September 30, 2018
- Announced $22 million PIPE financing led by Deerfield Management
  - Participation also from Perceptive Advisors, RA Capital, Fairmount and Proteon insiders
  - Deal closed in August 2017 and funds operations into Q1 2020
- 19.2 million shares outstanding + 22.1 million shares of unconverted preferred (an additional 4.6 million stock options outstanding)
- Ticker: PRTO (Nasdaq)

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