

VONAPANITASE (PRT-201, RECOMBINANT HUMAN TYPE I PANCREATIC ELASTASE) IMPROVED LONG-TERM RADIOCEPHALIC ARTERIOVENOUS FISTULA (RC AVF) PATENCY

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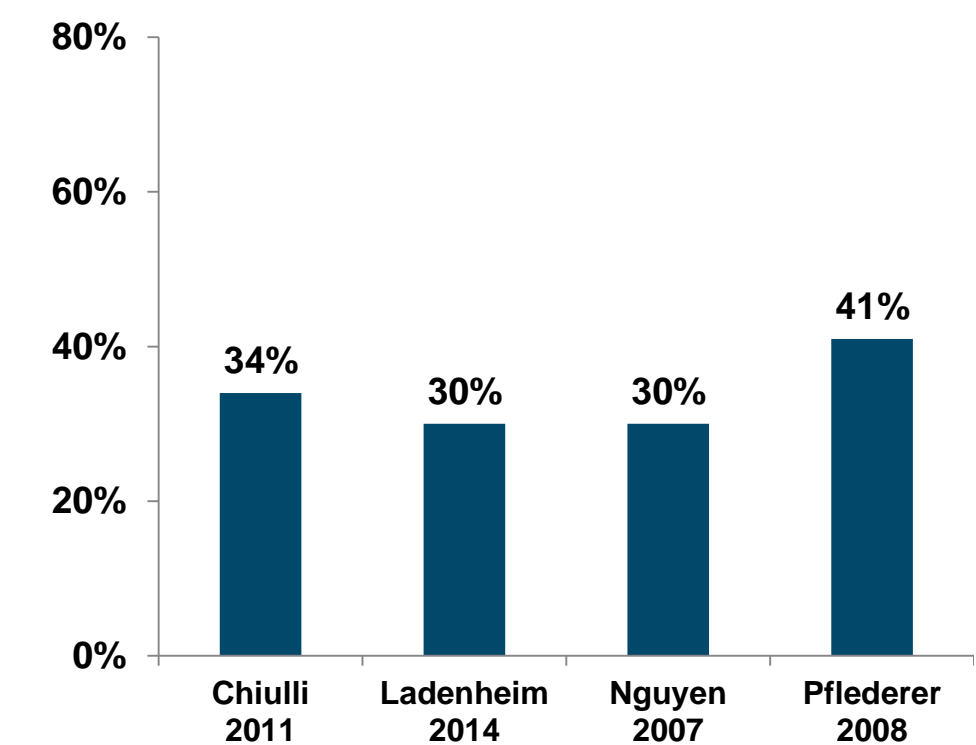
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Background

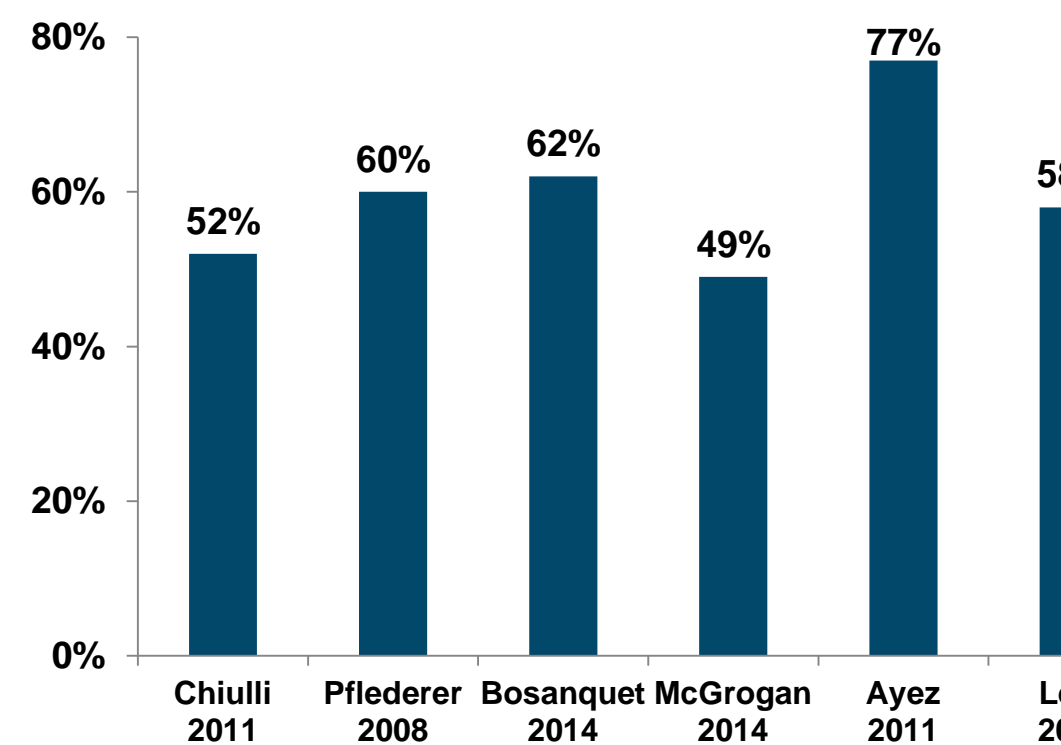
High Rates of AVF Maturation Failure and Patency Loss

- While radiocephalic AVFs (RC AVFs) are the preferred form of vascular access, most will fail within one year of surgical placement
 - Approximately 50% fail to adequately increase in lumen diameter and blood flow (maturation failure)
 - Approximately 70% thrombose or require an intervention (primary unassisted patency loss)
 - Approximately 35% are abandoned (secondary patency loss)
- Patients frequently endure repeated procedures and/or surgeries that also have a negative impact on providers

One-Year RC AVF Primary Patency (Recently Published Data)



One-Year RC AVF Secondary Patency (Recently Published Data)



Vonapanitase, an Investigational New Drug

Recombinant Human Elastase

- 26 kd serine protease
- Fragments elastin fibers
- Does not affect collagen fibers
- Localized effect
- Non-systemic
- Inactivated in blood by antiproteases



Single application to external surface of AVF immediately after surgical creation

Protocol

- Randomized, double-blind, placebo-controlled
- 151 subjects undergoing surgical creation of a radiocephalic AVF (RC AVF) or brachiocephalic AVF (BC AVF)
- Placebo, 10 and 30 mcg (1:1:1 randomization)
- Efficacy endpoints
 - Primary: primary unassisted patency
 - Secondary: unassisted maturation at 12 weeks, secondary patency, and AVF usability
- Follow-up at weeks 2, 6 and 12, and every 3 months thereafter
- Results of one-year analysis previously published (Hye 2014 *Journal of Vascular Surgery*)
 - Current analysis reported here occurred after last subject treated completed three years of follow-up
- Analyses of patency and the rate of procedures to restore/maintain patency by AVF type (RC AVF and BC AVF) and analyses excluding central stenosis were not pre-specified in the original study protocol

Human type I pancreatic elastase treatment of arteriovenous fistulas in patients with chronic kidney disease.
Hye R, Peden E, O'Connor T, et al. *Journal of Vascular Medicine and Biology*. 2014;26(1):1-10.
Ladenheim E, Lulich D, Lum C, et al. *First Week Postoperative Flow Measurements are Highly Predictive of Primary Patency of Radiocephalic Arteriovenous Fistulas*. Abstract from 2014 VASA Symposium. Nguyen TH, Bui TD, Gordon IL, et al. *Functional Patency of Autogenous AV Fistulas for Hemodialysis*. *J Vasc Access* 2007;8:275-280. Pflederer TA, Kwok S, Ketel BL, Pilgram T. *A Comparison of Transposed Brachiocephalic Fistulae With Nontransposed Fistulae and Grafts in the Fistula First Era*. *Semin Dial* 2008;21:357-63. Bosanquet DC, Rubasingham J, Imami M, et al. *Predicting Outcomes in Native AV Forearm Radiocephalic Fistulae: the CAVeA₂ Scoring System*. *J Vasc Access* 2015; 16:19-25. McGrogan DG, Maxwell AP, Inston NG, et al. *Preserving Arteriovenous Fistula Outcomes During Surgical Training*. *J Vasc Access* 2014;15:474-80. Ayez N, Fiole B, Aarts RA, et al. *Secondary Interventions in Patients with Autologous Arteriovenous Fistulas Strongly Improve Patency Rates*. *J Vasc Surg* 2011;54:1095-9. de Leur K, Öztürk C, Van Zeeeland M, et al. *Vascular Access Outcome in the Elderly Dialysis Patient in Combination With the Quality of Life*. *Vasc Endovascular Surg* 2013;47:444-8.

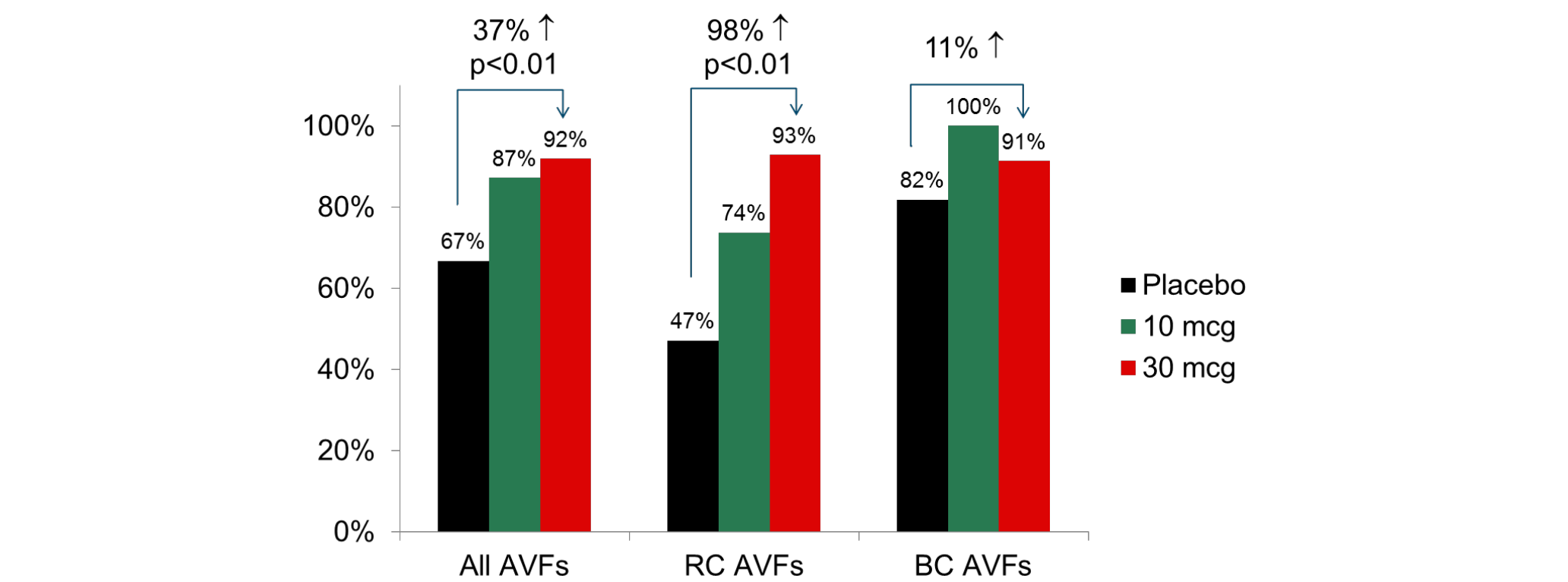
Demographics

	Placebo (n=51)	10 mcg (n=51)	30 mcg (n=49)
Male, %	63	55	55
White, %	63	78	74
Age, mean ± SD	59 ± 15	59 ± 18	59 ± 15
BMI, mean ± SD	31 ± 8	31 ± 8	35 ± 8
RC AVF, %	47	45	41
Pre-dialysis, %	57	55	71
CKD due to diabetes, %	39	43	55
CKD due to hypertension, %	35	28	22

Safety Results Over 3+ Years

- 151 received vonapanitase or placebo; at the time of analysis 63 are ongoing in the study, 40 had their AVFs abandoned, 48 terminated early (death (20), transplant (9), peritoneal dialysis (4), loss to follow-up (15))
- Average duration of follow-up at the time of this analysis is 21 to 23 months in the three groups
- No meaningful physical examination findings over 1 year
- No meaningful changes in safety laboratories (chemistry, hematology, coagulation) at 6 weeks
- Adverse events (AEs) consistent with medical conditions experienced by CKD patients undergoing AVF surgery
- For vonapanitase and placebo groups, AEs were comparable over 1 year and AEs related specifically to the AVF were comparable over 3+ years
- Safety results at one-year available in Hye 2014 *Journal of Vascular Surgery*

Unassisted Maturation at 12 Weeks



Unassisted maturation defined as average cephalic vein lumen diameter ≥ 4 mm and blood flow ≥ 500 mL/min at 12 weeks without prior patency loss.

Primary Unassisted and Secondary Patency

Percentage of Subjects Who Maintained Patency Over 3+ Years

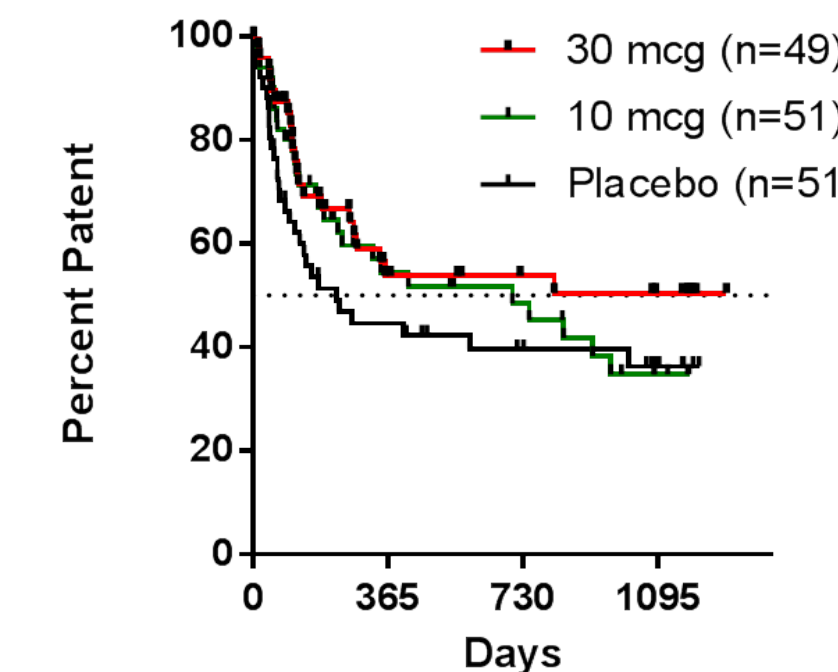
	Placebo	10 mcg	30 mcg
Primary Patency			
All AVFs (n=51,51,49)	36.3%	34.8%	50.4%
All Excl CS (n=51,51,49)	36.1%	41.3%	56.6%
RC AVFs (n=24,23,20)	31.1%	41.7%	62.7%
BC AVFs (n=27,28,29)	40.0%	29.1%	40.7%
BC Excl CS (n=27,28,29)	39.6%	40.6%	51.7%
Secondary Patency			
All AVFs (n=51,51,49)	63.0%	65.0%	76.9%
RC AVFs (n=24,23,20)	59.4%	74.7%	90.0%
BC AVFs (n=27,28,29)	66.3%	55.2%	67.2%

CS = central stenosis, RC AVF = radiocephalic arteriovenous fistula, BC AVF = brachiocephalic arteriovenous fistula.

Primary Unassisted Patency Over 3+ Years

All Subjects

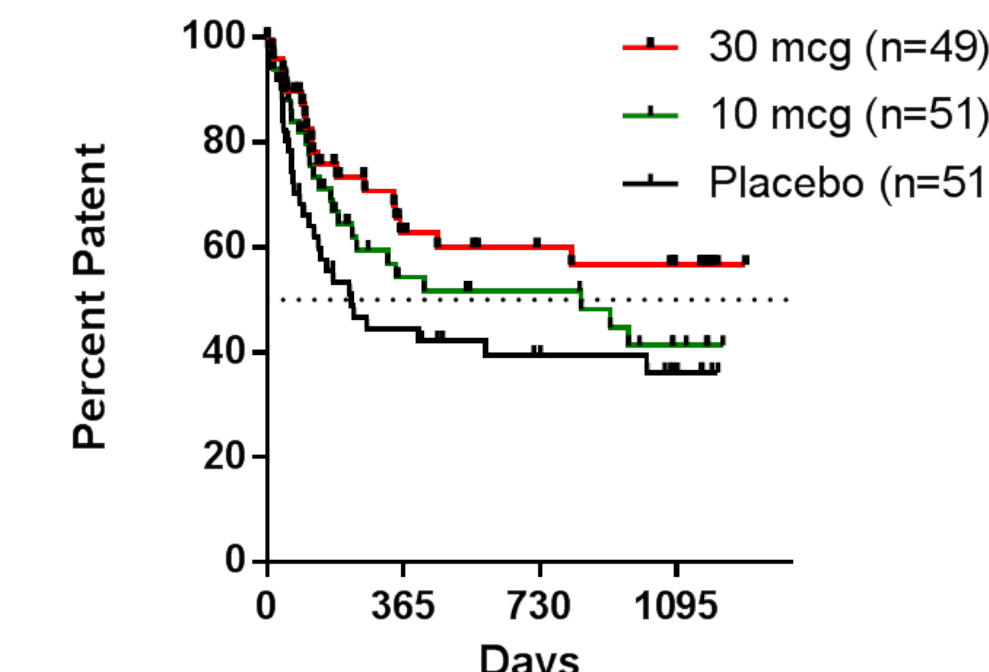
37% reduction (p=0.10) in the risk of primary patency loss for all subjects (30 mcg)



Primary unassisted patency defined as the time from AVF creation until the first occurrence of either access thrombosis or a procedure to restore or maintain patency.

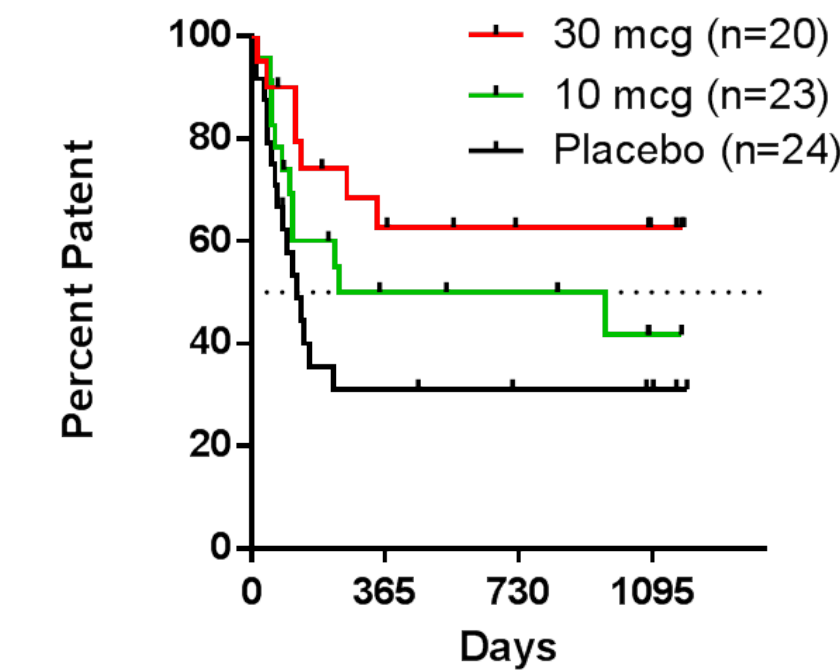
Excluding Central Stenosis

49% reduction (p=0.03) in the risk of primary patency loss when excluding central stenosis events as cause of patency loss (30 mcg)



Radiocephalic AVFs

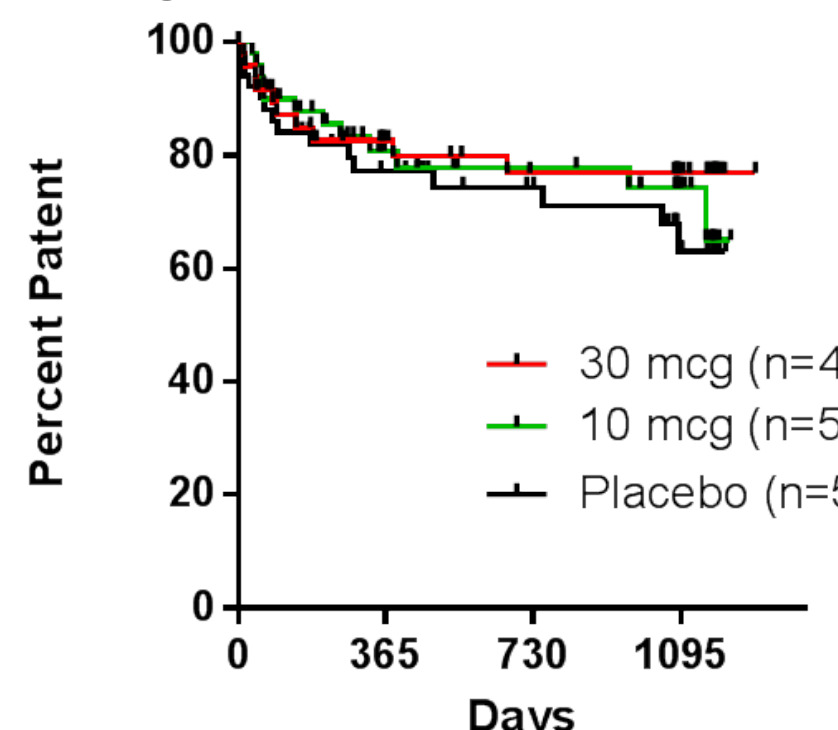
63% reduction (p=0.02) in the risk of primary patency loss for RC AVF subjects (30 mcg)



Secondary Patency Over 3+ Years

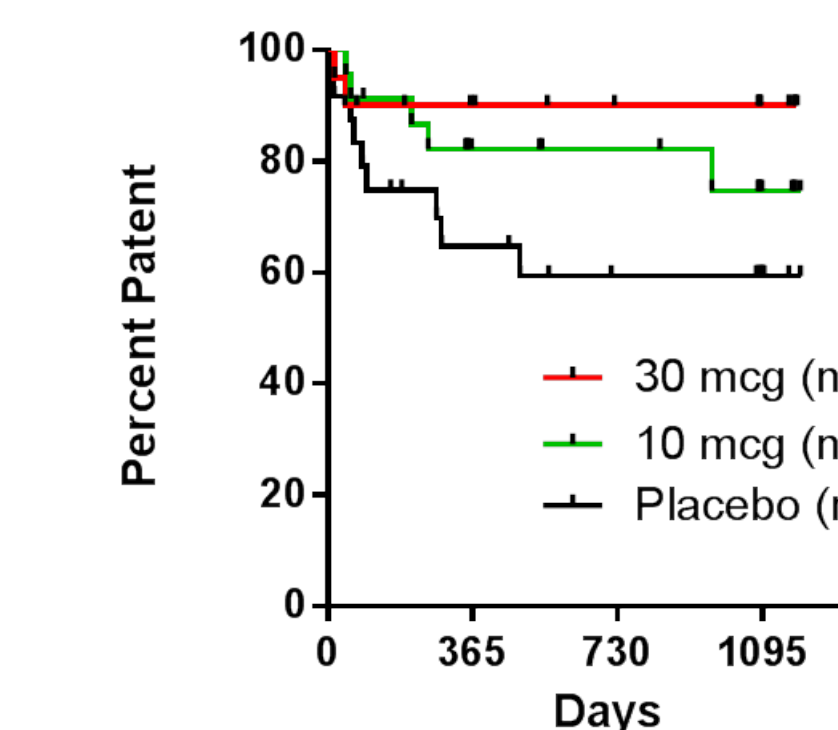
All Subjects

23% reduction (p=0.33) in the risk of secondary patency loss for all subjects (30 mcg)



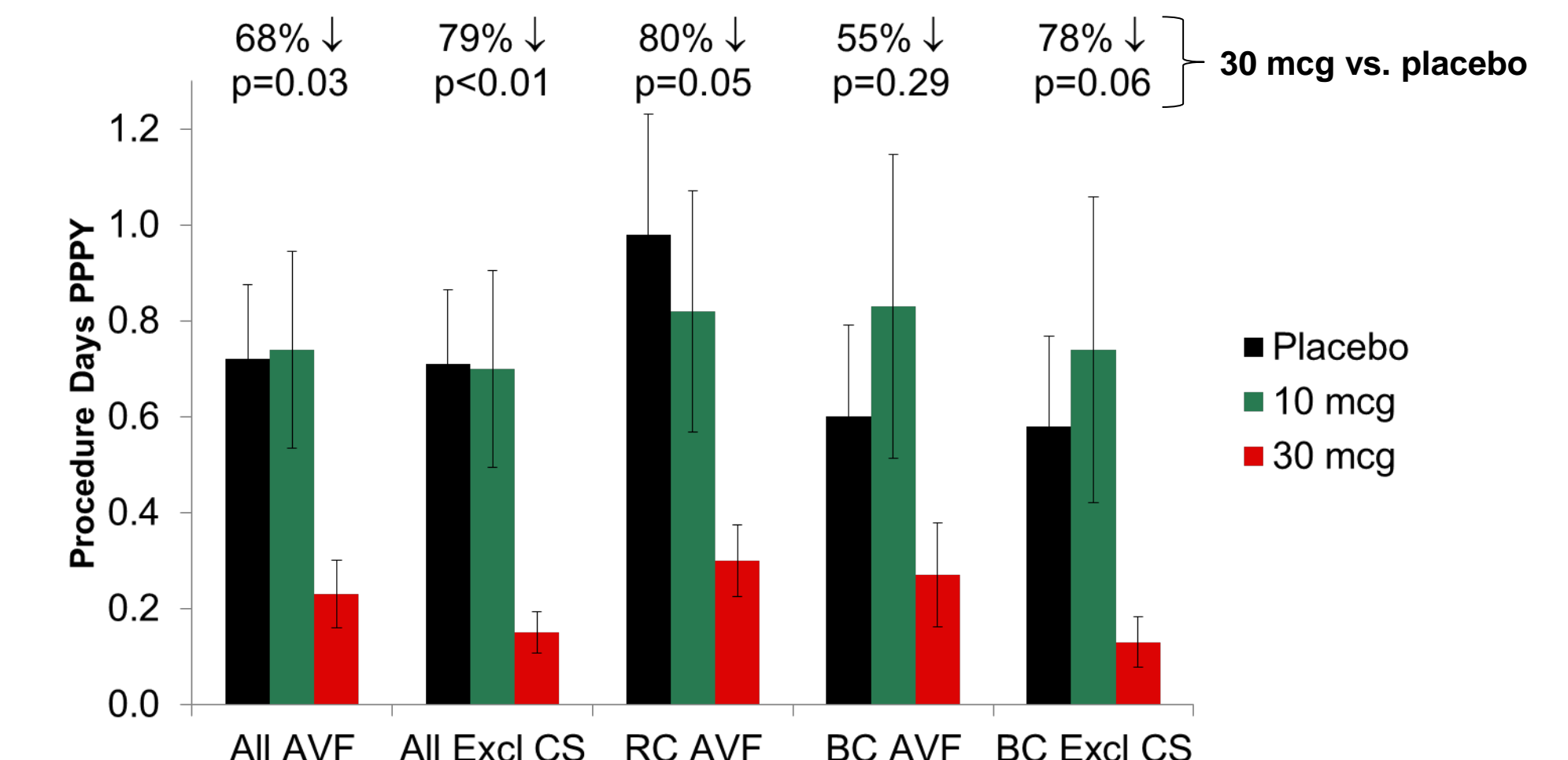
Radiocephalic AVFs

76% reduction (p=0.046) in the risk of secondary patency loss for RC AVF subjects (30 mcg)



Secondary patency defined as the time from AVF creation until AVF abandonment.

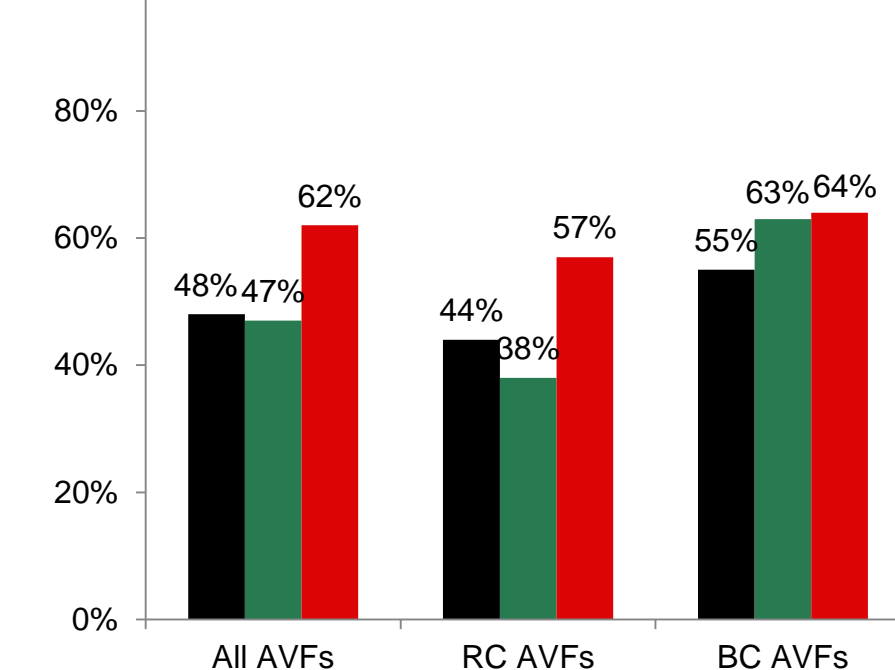
Procedures to Restore/Maintain Patency Over 3+ Years



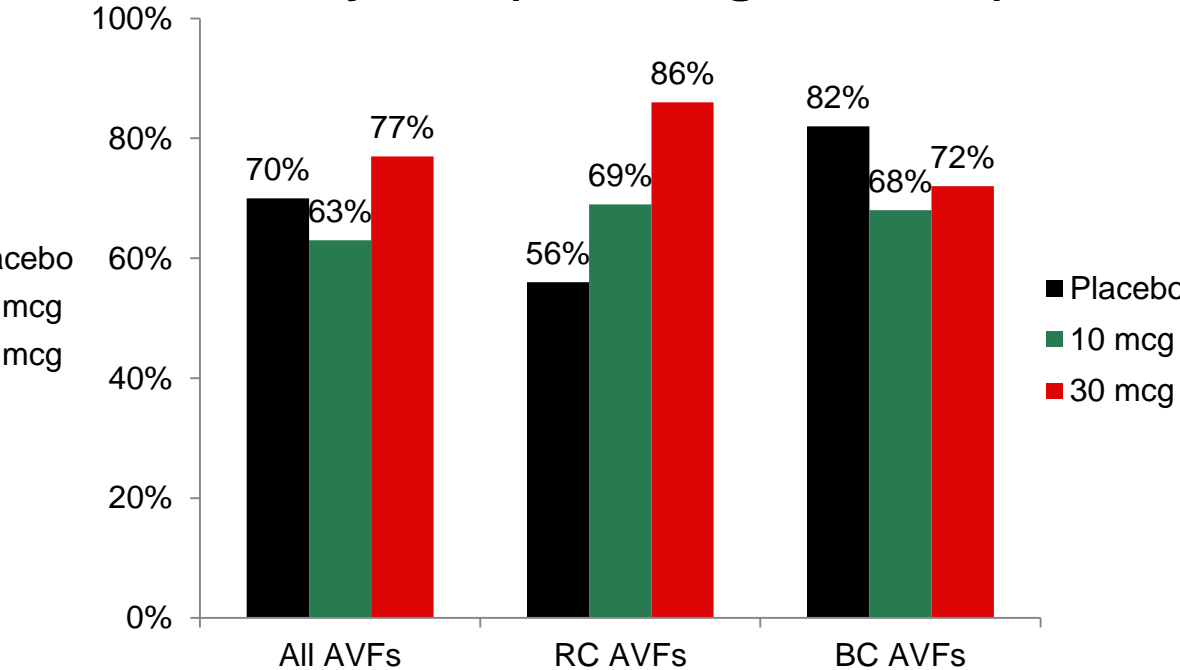
Mean number of days with a procedure to restore or maintain patency (thrombectomy, thrombolysis, percutaneous transluminal angioplasty, stent placement, or surgical revision). PPPY = per patient per year. +/- Standard Error.

AVF Use for Hemodialysis Over 3+ Years

Unassisted Use



Any Use (Including Assisted)



Unassisted Use defined as ≥90 days of consecutive use of the AVF without prior procedure to restore or maintain AVF patency. Any Use defined as ≥90 days of consecutive use of the AVF or ≥30 days of consecutive use in the event that the use began between the last and second to last study visits, independent of the need for procedures to restore or maintain patency. None of these differences were statistically significant.

Summary

- Results reported here are based on an analysis of over 3+ years of follow-up of a previously published study of one-year results (Hye 2014 *Journal of Vascular Surgery*).
- For vonapanitase and placebo groups, adverse events were comparable over 1 year and adverse events related specifically to the AVF were comparable over 3+ years.
- In subjects undergoing surgical creation of a RC AVF, vonapanitase treatment was associated with an improvement in unassisted maturation at 12 weeks and primary patency, secondary patency, and the rate of procedures to restore or maintain AVF patency over 3+ years. Vonapanitase treatment was also associated with an improvement in unassisted maturation at 12 weeks in the All AVFs group.
- Currently enrolling subjects in a randomized, double-blind, placebo-controlled phase 3 study in the United States (www.clinicaltrials.gov NCT02110901).

References

Hye R, Peden E, O'Connor T, et al. Human Type I Pancreatic Elastase Treatment of Arteriovenous Fistulae in Patients with Chronic Kidney Disease. *J Vasc Surg* 2014;60:454-461. Chiulli LC, Vasillas P, Dardik A. Superior Patency of Upper Arm Arteriovenous Fistulae in High Risk Patients. *J Sur Res* 2011;170:157-64. Ladenheim E, Lulich D, Lum C, et al. First Week Postoperative Flow Measurements are Highly Predictive of Primary Patency of Radiocephalic Arteriovenous Fistulas. Abstract from 2014 VASA Symposium. Nguyen TH, Bui TD, Gordon IL, et al. Functional Patency of Autogenous AV Fistulas for Hemodialysis. *J Vasc Access* 2007;8:275-280. Pflederer TA, Kwok S, Ketel BL, Pilgram T. A Comparison of Transposed Brachiocephalic Fistulae With Nontansposed Fistulae and Grafts in the Fistula First Era. *Semin Dial* 2008;21:357-63. Bosanquet DC, Rubasingham J, Imami M, et al. Predicting Outcomes in Native AV Forearm Radiocephalic Fistulae: the CAVeA₂ Scoring System. *J Vasc Access* 2015; 16:19-25. McGrogan DG, Maxwell AP, Inston NG, et al. Preserving Arteriovenous Fistula Outcomes During Surgical Training. *J Vasc Access* 2014;15:474-80. Ayez N, Fiole B, Aarts RA, et al. Secondary Interventions in Patients with Autologous Arteriovenous Fistulas Strongly Improve Patency Rates. *J Vasc Surg* 2011;54:1095-9. de Leur K, Öztürk C, Van Zeeeland M, et al. Vascular Access Outcome in the Elderly Dialysis Patient in Combination With the Quality of Life. *Vasc Endovascular Surg* 2013;47:444-8.