PATENCY-1: A Trial of Topically Applied Vonapanitase to Promote Radiocephalic Fistula Patency and Use for Hemodialysis

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Background

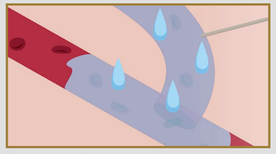
The arteriovenous fistula remains the preferred form of hemodialysis vascular access, providing a survival benefit compared to other forms of access. However, fistulas suffer from high rates of failure within one year of surgical creation:

- 40-60% experience a thrombosis or require a corrective procedure (primary patency loss)[1]
- 30-40% are abandoned (secondary patency loss)[1]
- 40-60% fail to be used for hemodialysis[2,3]

The radiocephalic fistula in the forearm is the preferred fistula location, but failure rates are higher than for upper arm fistula.[1]

Vonapanitase, an Investigational Drug

- 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 min) to the external surface of the fistula immediately after creation
- Active at site of application with no systemic effects observed since inactivated by blood



Single application to external surface of fistula after surgical creation

Protocol

Design	Multicenter, randomized, double-blind, placebo-controlled
N	313 patients at 31 U.S. centers
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 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

Demographics

	Vonapanitase (n=210)	Placebo (n=103)
Age - years	57 ± 14	57 ± 14
Weight - kg	100 ± 26	94 ± 25
BMI – kg/m^2	33 ± 8	32 ± 8
Male sex	174 (82.9)	76 (73.8)
Race or ethnic group		
Black	56 (26.7)	20 (19.4)
White	138 (65.7)	71 (68.9)
Preexisting condition		
Diabetes	126 (60.0)	58 (56.3)
Hypercholesterolemia	149 (71.0)	72 (69.9)
Hypertension	205 (97.6)	98 (95.1)
Congestive heart failure	62 (29.5)	29 (28.2)
Ischemic heart disease	60 (28.6)	32 (31.1)
Peripheral artery disease	31 (14.8)	12 (11.7)
Cerebrovascular disease	32 (15.2)	17 (16.5)
Chronic kidney disease		
Duration - months	54 ± 74	66 ± 85
Diabetes primary cause	90 (42.9)	40 (38.8)
Hypertension primary cause	49 (23.3)	26 (25.2)
Hemodialysis (HD) history		
On HD at randomization	94 (44.8)	43 (41.7)
Current central catheter	89 (42.4)	42 (40.8)
Fistula creation surgery		
Wrist	155 (73.8)	82 (80.4)
Forearm	51 (24.3)	19 (18.6)

Safety Results

- 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

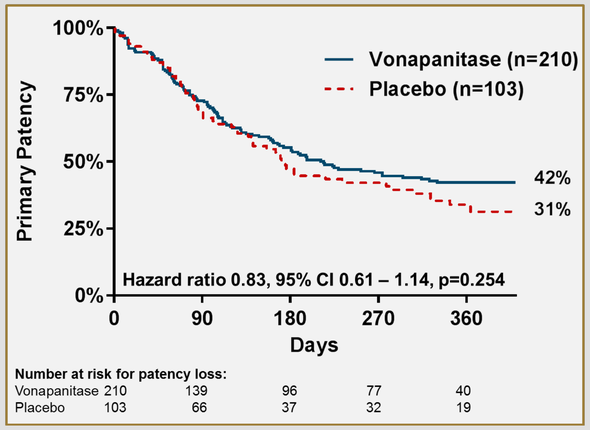
Adverse Events	Vonapanitase (n=209)	Placebo (n=102)
Vascular stenosis	38.3%	40.2%
Fistula thrombosis	19.6%	26.5%
Hypoaesthesia (numbness)	5.3%	4.9%
Procedural pain	4.8%	5.9%

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

Efficacy Results

Primary Patency

Primary patency defined as time from fistula surgical creation until first thrombosis or procedure to restore or maintain patency.

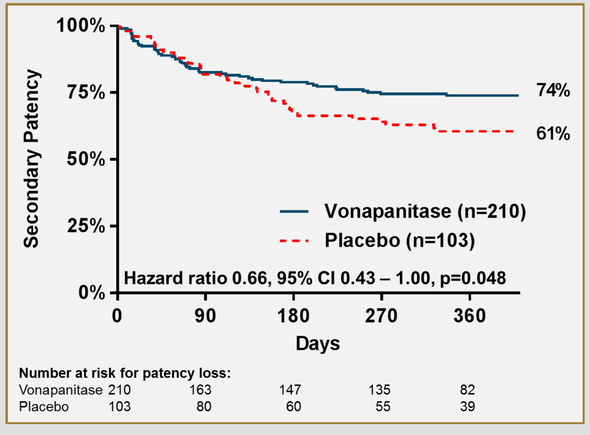


Number at risk for patency loss:

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

Secondary Patency

Secondary patency defined as time from fistula surgical creation until fistula abandonment.



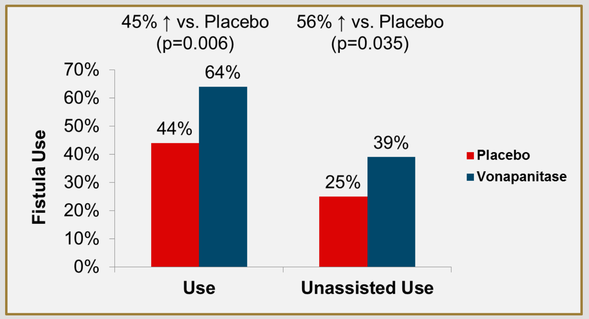
Number at risk for patency loss:

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

Efficacy Results (cont.)

Use for Hemodialysis

Use was defined as the ability of the fistula to be successfully cannulated with 2 needles for a minimum of 90 days or at least 30 days and in use at the patient's last visit if hemodialysis had not been initiated at least 90 days prior to the last visit. Unassisted use defined as use without a prior procedure to restore or maintain patency.



Efficacy Population Analysis

Pre-specified analysis excluding 29 patients (19 vonapanitase, 10 placebo) who had primary or secondary patency loss or early termination by week 2 visit.

- Primary patency at 12 months was 46% for vonapanitase and 34% for placebo (HR 0.80; 95% CI 0.57-1.12, p=0.187)
- Secondary patency was 80% for vonapanitase and 64% for placebo (HR 0.52; 95% CI 0.32-0.85, p=0.007)
- Use for hemodialysis was 71% for vonapanitase and 48% for placebo (p=0.001)

Summary

- Vonapanitase did not show a significant improvement in primary patency in patients undergoing radiocephalic fistula creation.
- Vonapanitase was associated with significant improvements in secondary patency and fistula use for hemodialysis.

Status

Ongoing PATENCY-2 study of vonapanitase evaluating co-primary endpoints of secondary patency and fistula use for hemodialysis in patients undergoing surgical creation of a radiocephalic fistula.

References

1. Al-Jaishi et al. Patency rates of the arteriovenous fistula for hemodialysis: a systematic review and meta-analysis. Am J Kidney Dis 2014;63:464-478.
2. Dember et al. Effect of Clopidogrel on Early Failure of Arteriovenous Fistulas for Hemodialysis. JAMA 2008;299(18):2164-2171.
3. Irish AB al. Effect of fish oil supplementation and aspirin use on arteriovenous fistula failure in patients requiring hemodialysis: A randomized clinical trial. JAMA Intern Med 2017;177:184-193.