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ABSTRACT

Objective: This study explored the long-term outcomes of arteriovenous fistulas treated with vonapanitase (recombinant human elastase) at the time of surgical creation.

Methods: This was a randomized, double-blind, placebo-controlled trial of 151 patients undergoing radiocephalic or brachiocephalic arteriovenous fistula creation who were randomized equally to placebo, vonapanitase 10 μg, or vonapanitase 30 μg. The results after 1 year of follow-up were previously reported. The current analysis occurred when the last patient treated was observed for 3 years. For the current analysis, the primary end point was primary patency; the secondary end points included secondary patency, use of the fistula for hemodialysis, and rate of procedures to restore or to maintain patency.

Results: There was no significant difference in the risk of primary patency loss with vonapanitase 10 μg or 30 μg vs placebo. When seven initial patency loss events related to cephalic arch and central vein balloon angioplasty were excluded, the risk of patency loss was reduced with vonapanitase overall (hazard ratio [HR], 0.63; $P = .049$) and 30 μg (HR, 0.51; $P = .03$). In patients with radiocephalic fistulas (n = 67), the risks of primary and secondary patency loss were reduced with 30 μg (HR, 0.37 [$P = .02$] and 0.24 [$P = .046$], respectively). The rate of procedures to restore or to maintain fistula patency was reduced with 30 μg vs placebo (0.23 vs 0.72 procedure days/patient/year; $P = .03$) and also reduced in patients with radiocephalic fistulas with 30 μg vs placebo (0.17 vs 0.85 procedure days/patient/year; $P = .048$).

Conclusions: In this study, vonapanitase did not significantly improve primary patency in the primary analysis but did significantly improve primary patency in an analysis that excluded patency loss due to cephalic arch and central vein balloon angioplasty. In patients with radiocephalic fistulas, 30 μg significantly improved primary and secondary patency. Vonapanitase 30 μg decreased the rate of procedures to restore or to maintain patency in the analysis that included all patients and in the subset with radiocephalic fistulas. (J Vasc Surg 2017;65:1113-20.)

A functional arteriovenous fistula (AVF) is the preferred form of hemodialysis vascular access because of superior patency and reduced need for corrective procedures compared with other forms of access.[1,2] However, AVFs often fail to mature and frequently experience loss of primary unassisted patency (primary patency).[1,3,4] Patency loss is typically the result of stenosis formation due to neointimal hyperplasia and is manifested as AVF thrombosis or diminished AVF blood flow, resulting in inadequate hemodialysis and the need for interventional or surgical procedures.[1] Many AVFs also experience loss of secondary patency, defined as AVF abandonment.[3,4]

Vonapanitase (formerly PRT-201) is a recombinant human chymotrypsin-like elastase family member 1 (CELA1).[5] Vonapanitase is applied topically to the external adventitial surface of the surgically exposed inflow artery, anastomosis, and outflow vein immediately after AVF creation with the intent of improving AVF maturation and patency. Vonapanitase locally fragments the protein elastin in elastic fibers present in the blood vessel walls, liberating peptide fragments that may be chemoattractants for the cells that participate in the formation of intimal hyperplasia.[6-8]

A previous clinical trial suggested that vonapanitase at doses of 0.0033 to 0.033 mg may decrease hemodynamically significant AVF lumen stenosis, decrease the need for balloon angioplasty, and prolong AVF primary patency.[9] On the basis of these promising findings, two vonapanitase doses, 0.01 mg and 0.03 mg (10 μg and 30 μg), were selected for investigation in the current randomized, double-blind placebo-controlled trial in patients undergoing placement of a radiocephalic or brachiocephalic AVF. The primary efficacy analysis at 1 year was previously published.[10] In that analysis, vonapanitase 30 μg was associated with a significant improvement in unassisted maturation at 3 months by duplex Doppler ultrasound imaging. Vonapanitase 30 μg was also associated with a nonsignificant 33% decrease in the risk of primary patency loss and a significant 63% decrease in the risk of primary patency loss in patients with radiocephalic AVFs. Patients completing the 12 months of follow-up entered a registry to track long-term outcomes. Here we present the results of an efficacy analysis after an additional 2 years of follow-up. The aim was to describe the long-term effects of vonapanitase treatment on clinically relevant end points such as patency and use of the AVF for hemodialysis.

METHODS

This study was a prospective, observational follow-up of a randomized, double-blind, placebo-controlled trial. A full list of participating centers and the number of patients treated at each can be found in the Acknowledgments. The protocol, informed consent form, and all amendments were reviewed and approved by each center's Institutional Review Board. This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and current Good Clinical Practices and in compliance with the Code of Federal Regulations (21 CFR 312). All patients who participated signed an informed consent document. The trial was preregistered at www.clinicaltrials.gov and enrolled patients with chronic kidney disease who were on hemodialysis or planning to initiate hemodialysis within 6 months and were undergoing creation of a radiocephalic or brachiocephalic AVF. Exclusion criteria were age <18 years, life expectancy <6 months, pregnancy, history of arterial aneurysm, previous treatment with vonapanitase, malignant disease, and significant liver disease. Selection of the AVF location was left to the surgeon. Because radiocephalic and brachiocephalic AVFs were allowed, it was assumed the surgeon would choose the best access for each patient based on the patient's characteristics including the results of vein mapping, which was standard of care.

Patients were randomized equally into one of three dose groups—placebo, 10 μg, or 30 μg—using block sizes of six. Vonapanitase was provided as a lyophilized powder in 5-mg vials that were reconstituted with

Table I. Baseline characteristics

	Placebo (n = 51)	Vonapanitase 10 μg (n = 51)	Vonapanitase 30 μg (n = 49)
Male	32 (63)	28 (55)	27 (55)
White	32 (63)	40 (78)	36 (74)
Age, years	59 ± 15	59 ± 18	59 ± 15
≥65 years	18 (35)	23 (45)	15 (31)
BMI,[a] kg/m²	31 ± 8	31 ± 8	35 ± 8
RC AVF	24 (47)	23 (45)	20 (41)
IHD	25 (49)	30 (59)	28 (57)
PAD	15 (29)	10 (20)	11 (22)
CVD	9 (18)	11 (22)	11 (22)
On hemodialysis	22 (43)	23 (45)	14 (29)
Central venous catheter	22 (43)	21 (41)	16 (33)
Ipsilateral central venous catheter	5 (10)	4 (8)	4 (8)
CKD secondary to DM	20 (39)	22 (43)	27 (55)
CKD secondary to HTN	18 (35)	14 (27)	11 (22)
Duration of CKD, months	44 ± 44	54 ± 66	60 ± 75

AVF, Arteriovenous fistula; *BMI,* body mass index; *CKD,* chronic kidney disease; *CVD,* cerebrovascular disease; *DM,* diabetes mellitus; *HTN,* hypertension; *IHD,* ischemic heart disease; *PAD,* peripheral artery disease; *RC,* radiocephalic.
Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation.
[a]Unpaired *t*-test, P < .01.

phosphate-buffered saline containing 0.01% polysorbate 80 and diluted to final concentrations of 4 or 12 μg/mL by an unblinded research pharmacist. The placebo was the reconstitution fluid and was identical in appearance to the vonapanitase solution. Immediately after creation of the AVF, a 2.5-mL solution was topically applied as a series of drops during 10 minutes to the exposed inflow artery, anastomosis, and outflow vein including the mobilized vein swing segment, after which the area was lavaged for 1 minute with saline solution. After surgery and drug administration, in-person visits occurred at weeks 2 and 6 and months 3, 6, 9, and 12. Thereafter, patients were contacted every 3 months either by in-person visits or by a phone call to the patient, the patient's family, or caregivers. The treatment assignment remained double-blinded until the month 12 visit, after which the study sponsor (Proteon Therapeutics) was unblinded. The trial teams and patients remained blinded to treatment assignment throughout the entire follow-up period. Follow-up ended at the time of the analysis for patients still active in the study, when a patient's AVF was abandoned, or at the last study visit for patients who terminated early (died, received a kidney transplant, switched to peritoneal dialysis, withdrew consent, or were lost to follow-up). Data collected
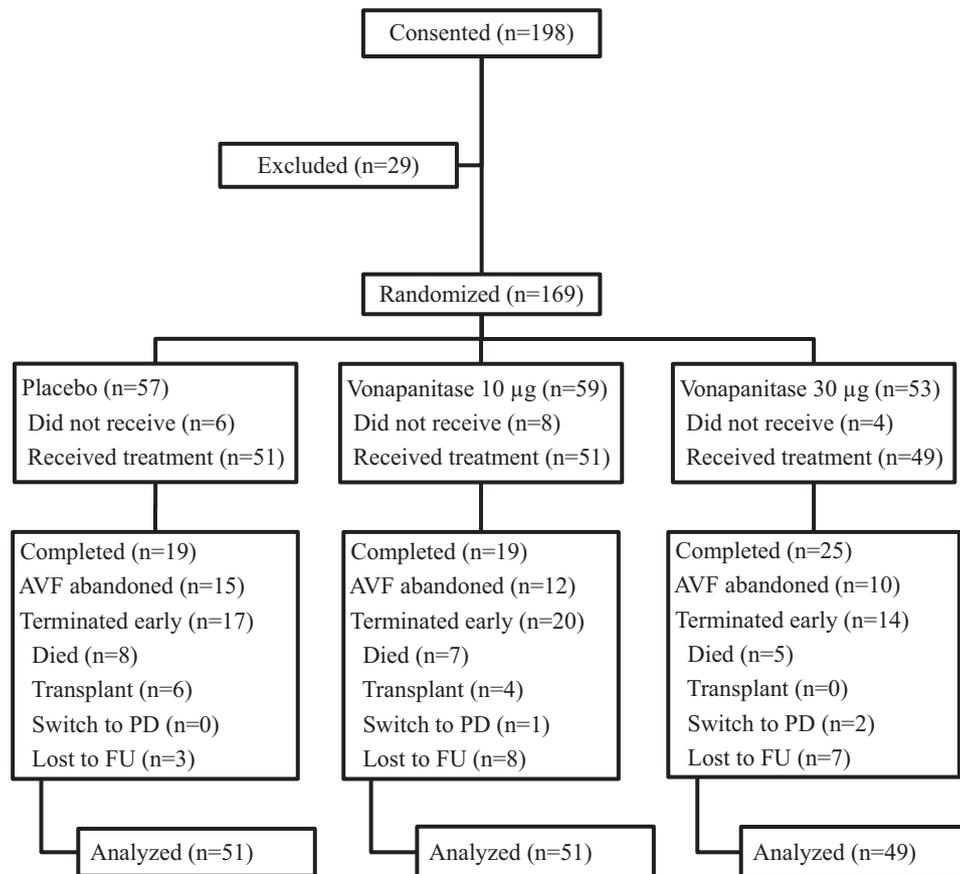
Fig 1. Flow of patients through the study. *AVF*, Arteriovenous fistula; *FU*, follow-up; *PD*, peritoneal dialysis.

included adverse events (all events until week 6, then events related to the arm with the AVF until month 12); physical examinations (general examination before surgery and at week 6 and AVF arm examination at all visits to month 12); duplex Doppler ultrasound examinations (week 6 and month 3); and safety laboratory determinations, including a chemistry panel, complete blood cell count, and antivonapanitase antibodies (before surgery and at week 6). In addition, the date of hemodialysis initiation, AVF use for hemodialysis, reasons for nonuse, reasons for AVF abandonment, complications associated with the AVF, and procedures performed on the AVF were collected for the entire follow-up period. A previous publication reported the results of analyses conducted through month 12.[10] The current analysis was completed after the last patient treated was observed for a total of 3 years. The primary efficacy end point was primary patency, defined as the time from AVF creation until first occurrence of either AVF thrombosis detected by physical examination or imaging or an invasive procedure to restore or to maintain AVF patency including thrombectomy, thrombolysis, balloon angioplasty, stent placement, and surgical revision. Procedure reports were reviewed to confirm accurate reporting.

Secondary efficacy end points included secondary patency (time from AVF creation to abandonment), procedure rate (total number of days on which invasive procedures were performed to the AVF, divided by post-treatment follow-up time), and AVF use for hemodialysis. AVF use for hemodialysis was defined as use of the trial AVF for hemodialysis for ≥3 months. If hemodialysis was not initiated at least 3 months before the end of the study, successful use was defined as use for at least 1 month and in use at the patient's last study visit. Nonuse was defined as AVF abandonment before cannulation or hemodialysis for two consecutive trial visits (≥3 months apart) without use of the trial AVF. Unassisted use was defined as AVF use for hemodialysis without any prior procedures performed to restore or to maintain AVF patency. Assisted use was defined as AVF use for hemodialysis with at least one prior procedure performed to restore or to maintain AVF patency. Any use was the sum of unassisted and assisted use.

For powering, it was assumed that 50% of placebo patients, 80% of patients receiving 10 µg, and 80% of patients receiving 30 µg would retain AVF primary patency, equating to a hazard ratio (HR) of 0.32 (ie, a 68% reduction in risk of primary patency loss). Group sizes of 50 provided 80% power using a two-sided
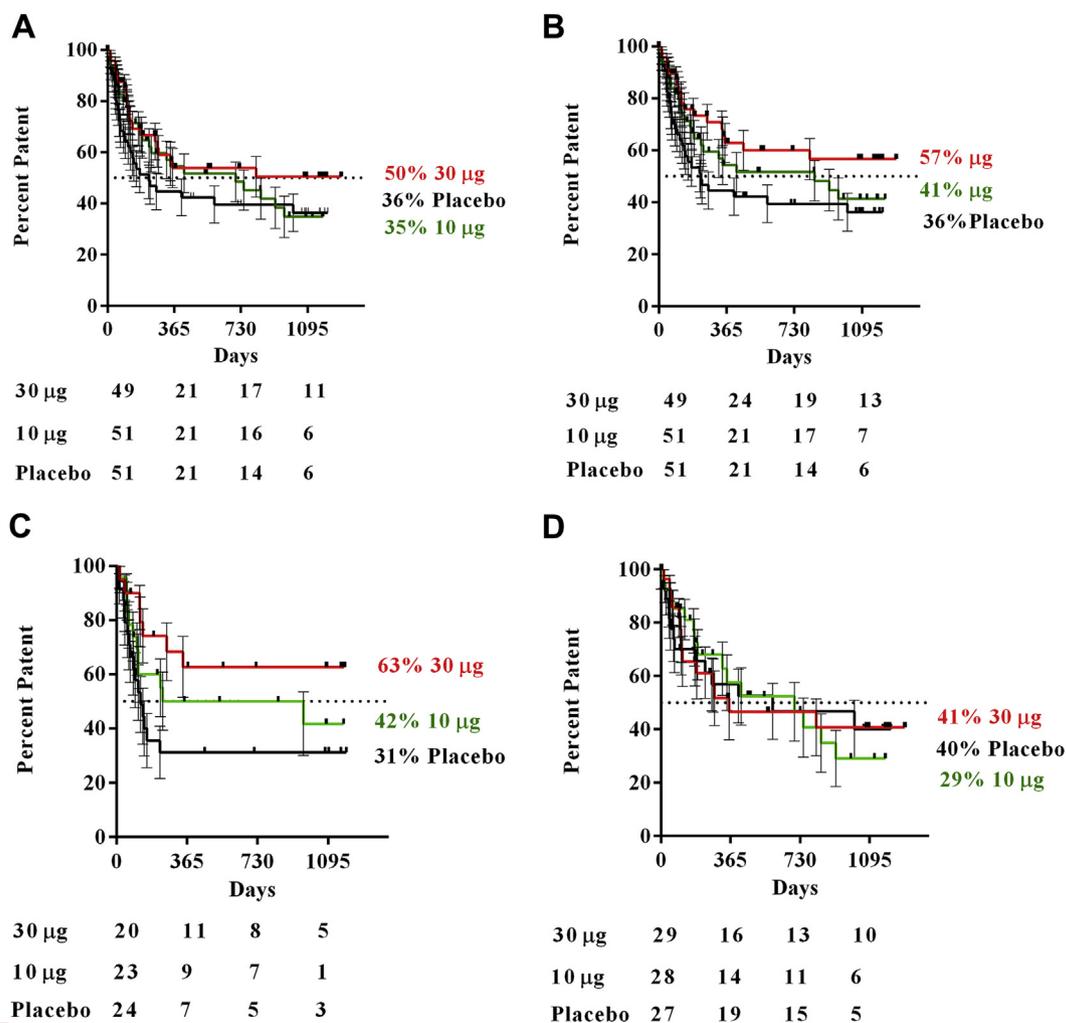
Fig 2. Arteriovenous fistula (AVF) primary patency: *red,* vonapanitase 30 μg; *green,* vonapanitase 10 μg; *black,* placebo. **A,** All AVFs. **B,** All AVFs excluding patency loss events due to angioplasty of cephalic arch or central vein stenosis. **C,** Radiocephalic AVFs. **D,** Brachiocephalic AVFs.

log-rank test assuming $\alpha = .05$. Primary patency time was estimated using Kaplan-Meier life test methods. Patients without primary patency loss were censored at the date of the last visit. The HR for each vonapanitase dose vs placebo was calculated using a Cox proportional hazards model including treatment as the covariate. A sensitivity analysis was conducted that excluded primary patency loss events solely due to balloon angioplasty of cephalic arch or central vein stenosis. In this sensitivity analysis, the affected patients remained at risk for primary patency loss due to subsequent AVF thrombosis or procedures to restore or to maintain patency in the arm with the AVF.

Analyses similar to those described for primary patency were performed for secondary patency (ie, Kaplan-Meier life test methods, log-rank tests, and Cox proportional hazards including treatment as the covariate). The number of days on which patients had procedures was summarized, and procedure days per patient per year

were calculated; the groups were compared with a Wilcoxon rank sum test. The number and percentage of patients with successful use of the AVF for hemodialysis were summarized and tested using a χ^2 test. Patients who never initiated dialysis were excluded. All analyses were repeated for patients who underwent creation of radiocephalic AVFs and separately for brachiocephalic AVFs. All statistical analyses were performed using SAS software, version 9.2 or higher (SAS Institute, Cary, NC).

RESULTS

There were 151 patients enrolled between April 2011 and November 2012. Table I summarizes the patients' baseline characteristics. None of the differences between groups were statistically significant with the exception of body mass index, which was highest in the 30-μg group. The current analysis was performed when the last patient treated was observed for 3 years, which occurred in November 2015. At the time of analysis,
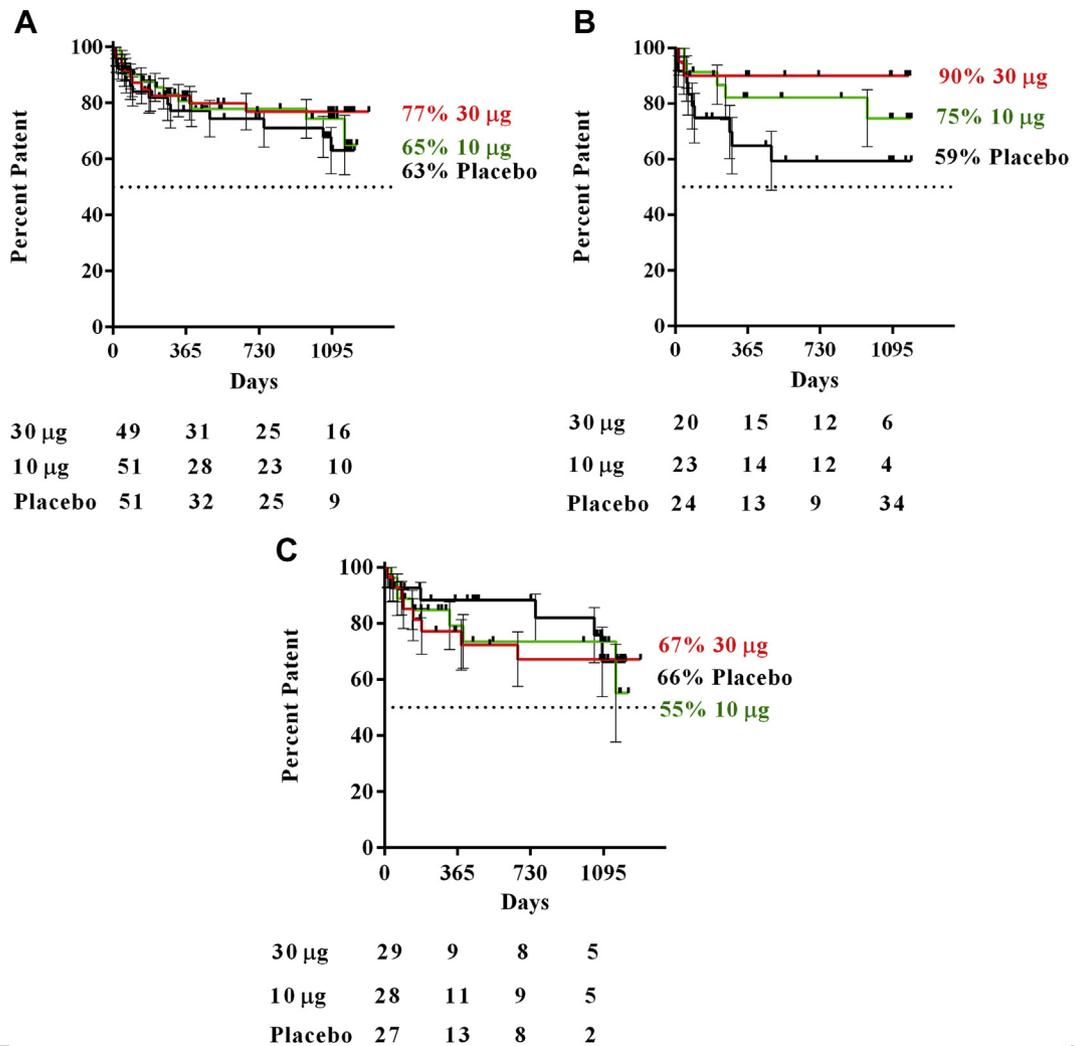
Fig 3. Arteriovenous fistula (AVF) secondary patency: *red*, vonapanitase 30 μg; *green*, vonapanitase 10 μg; *black*, placebo. **A,** All AVFs. **B,** Radiocephalic AVFs. **C,** Brachiocephalic AVFs.

median post-treatment follow-ups were 633, 537, and 1079 days for placebo, 10 μg, and 30 μg, respectively. Fewer patients in the 30-μg group had the AVF abandoned or terminated early compared with the placebo and 10-μg groups, explaining the differences in median follow-up times (Fig 1). Because of AVF abandonments and early terminations, there were a small number of subjects at risk during the later years of follow-up. As a result, the Kaplan-Meier curves should be interpreted with caution at these later time points, especially in the subsets by AVF type.

Median primary patency time (the time at which >50% of patients in a group lost patency) was more than three-fold longer with vonapanitase than with placebo (746 vs 224 days, respectively; Fig 2, A). However, the risk of primary patency loss was not significantly reduced vs placebo for 10 μg (HR, 0.81; 95% confidence interval [CI], 0.48-1.36; P = .42) or 30 μg (HR, 0.63; 95% CI, 0.36-1.10; P = .10) or for vonapanitase overall (HR, 0.71; 95% CI,

0.45-1.13; P = .14). In the analysis excluding balloon angioplasty procedures directed at cephalic arch and central vein stenosis in seven patients with brachiocephalic AVFs (Fig 2, B), the risk of primary patency loss was significantly reduced vs placebo for 30 μg (HR, 0.51; 95% CI, 0.28-0.93; P = .03) and for vonapanitase overall (HR, 0.63; 95% CI, 0.39-1.01; P = .049) but not for vonapanitase 10 μg.

Among patients with radiocephalic AVFs, median primary patency time was 125 days and 967 days with the placebo and 10-μg groups and >1181 days with the 30-μg and vonapanitase overall groups (Fig 2, C). In this subgroup, the risk of primary patency loss was significantly reduced vs placebo for both 30 μg (HR, 0.37; 95% CI, 0.15-0.91; P = .02) and vonapanitase overall (HR, 0.51; 95% CI, 0.26-0.99; P = .04). The risk of primary patency loss was not significantly reduced for 10 μg. In patients with brachiocephalic AVFs, there were no significant differences in primary patency in the primary analysis or in

Table II. Rate of procedures to restore or to maintain patency per patient per year on trial

Variable[a]	Placebo (n = 51)	Vonapanitase 10 μg[b] (n = 50)	P value[c]	Vonapanitase 30 μg[b] (n = 48)	P value[c]
All AVFs					
No.	51	50		48	
All AVFs	0.72 (1.11)	0.74 (1.45)	.93	0.23 (0.49)	.03
All AVFs, excluding cephalic arch and central vein procedures	0.71 (1.10)	0.70 (1.45)	.70	0.15 (0.30)	.01
RCF					
No.	24	23		20	
RCF	0.85 (1.23)	0.64 (1.20)	.60	0.17 (0.34)	.048
RCF, excluding cephalic arch and central vein procedures	0.85 (1.23)	0.64 (1.20)	.60	0.17 (0.34)	.048
BCF					
No.	27	27		28	
BCF	0.60 (1.00)	0.83 (1.6)	.69	0.27 (0.57)	.29
BCF, excluding cephalic arch and central vein procedures	0.58 (0.98)	0.74 (1.66)	1.00	0.13 (0.28)	.06

AVF, Arteriovenous fistula; *BCF,* brachiocephalic fistula; *RCF,* radiocephalic fistula.
Values are reported as mean (standard deviation).
[a]Procedure days rate to restore or to maintain patency per year at risk defined as the total number of procedure days to restore or to maintain patency/time on trial.
[b]Excludes one subject in the 10-μg group and one subject in the 30-μg group who discontinued on day 1 without any procedure data.
[c]P values vs placebo from a Wilcoxon rank sum test.

the analysis excluding balloon angioplasty procedures directed at cephalic arch or central vein stenosis (Fig 2, *D*).

The median secondary patency time was not reached in any dose group (Fig 3, *A*) as less than half of patients had their AVF abandoned in any group. Overall, the risk of secondary patency loss was not significantly reduced vs placebo for 10 μg (HR, 0.79; 95% CI, 0.37-1.68; $P = .54$), 30 μg (HR, 0.68; 95% CI, 0.30-1.50; $P = .33$), or vonapanitase overall (HR, 0.73; 95% CI, 0.38-1.40; $P = .34$). However, in patients with radiocephalic AVFs, the risk of secondary patency loss was significantly reduced vs placebo for 30 μg (HR, 0.24; 95% CI, 0.05-1.10; $P = .046$) and vonapanitase overall (HR, 0.38; 95% CI, 0.14-1.01; $P = .04$); the risk of secondary patency loss with 10 μg vs placebo was not significant in this subgroup (Fig 3, *B*). Findings among patients with brachiocephalic AVFs were similar to those seen for patients overall (Fig 3, *C*).

At least one procedure to restore or to maintain AVF patency was performed for 47% (24/51), 48% (24/50), and 29% (14/48) of patients in the placebo, 10-μg, and 30-μg groups, respectively. The procedure rate per patient per year was significantly reduced with 30 μg vs placebo (0.23 vs 0.72; $P = .03$) and also in patients with radiocephalic AVFs (0.17 vs 0.85; $P = .048$; Table II). Similar findings were seen when balloon angioplasty procedures directed at cephalic arch and central vein stenosis were excluded. At the 10-μg dose and in patients with brachiocephalic AVFs, no significant differences vs placebo were seen.

No statistically significant differences were seen with regard to achievement of unassisted use or any

successful use of the AVF for hemodialysis (Table III). Findings were similar in patients with radiocephalic and brachiocephalic AVFs (Table III). In patients with radiocephalic AVFs, there tended to be a higher proportion with any use of the AVF for hemodialysis with 30 μg vs placebo (80% vs 56%; $P = .14$).

Safety results during the first 12 months were previously reported, and there were no statistically significant differences in adverse events between treatment groups.[7] During the registry (ie, after the month 12 visit), medical events of interest related to the AVF (infection, aneurysm, pseudoaneurysm, and thrombosis) were reported in six placebo patients (19%) and five vonapanitase patients (8%). Aneurysm was reported in three placebo patients (9%) and no vonapanitase patients.

DISCUSSION

In this study, no significant differences were seen between active treatment and placebo with regard to primary patency time. However, when patency loss events due to cephalic arch and central vein balloon angioplasty were excluded, there was a significant difference in primary patency for vonapanitase overall and 30 μg vs placebo. Stenosis in the cephalic arch or central veins is far removed from the treatment site and thus is unlikely to be modified by local treatment of vonapanitase, which is inactivated by blood and thus acts only at the site of application.[11] Overall, vonapanitase-treated patients had a lower rate of procedures to restore or to maintain patency vs placebo, with a significant difference between 30 μg and placebo, and the relative

Table III. Percentages with arteriovenous fistula (AVF) use for hemodialysis[a]

	Placebo	Vonapanitase 10 μg	Vonapanitase 30 μg
All AVFs	n = 51	n = 51	n = 49
Unassisted use—yes	20 (50)	19 (51)	24 (60)
Any use[b]—yes	28 (70)	25 (68)	30 (75)
Indeterminate[c]	11	14	9
RCF	n = 24	n = 23	n = 20
Unassisted use—yes	5 (28)	5 (29)	8 (53)
Any use[b]—yes	10 (56)	12 (68)	12 (80)
Indeterminate[c]	6	6	5
BCF	n = 27	n = 28	n = 29
Unassisted use—yes	12 (55)	12 (60)	16 (64)
Any use[b]—yes	18 (82)	13 (65)	18 (72)
Indeterminate[c]	5	8	4

BCF, Brachiocephalic fistula; *RCF,* radiocephalic fistula.
Values are reported as No. (%).
[a]Excludes patients with indeterminate use (ie, those with a patent AVF who never initiated hemodialysis) from the denominator for percentage calculation.
[b]Any use includes unassisted and assisted use (meaning procedures to restore or to maintain patency of the AVF before use).
[c]Use or nonuse could not be determined because of not being on hemodialysis and not having had the AVF abandoned.

reduction was even greater when balloon angioplasty procedures directed at cephalic arch and central vein stenosis were excluded. The vonapanitase treatment effect was greater in those with radiocephalic AVFs than in those with brachiocephalic AVFs. Radiocephalic AVFs typically fail because of stenosis, occurring predominantly in the perianastomotic area, an area within the treatment zone of vonapanitase, which may explain the superior efficacy of vonapanitase in this AVF type.[12,13]

Vonapanitase fragments elastin in the vessel adventitia, liberating peptide fragments. Studies with a porcine homologue of vonapanitase have shown that elastin fragments are chemoattractants for cells that participate in the formation of intimal hyperplasia.[6-8] Peptide fragments created in the adventitia may retain scar-forming cells in the adventitia, thereby decreasing migration to the lumen and lumen stenosis after vessel injury.[14,15] In a previous publication of data from this trial, duplex Doppler ultrasound examinations showed less hemodynamically significant stenosis in vonapanitase-treated AVFs.[10] In the radiocephalic AVFs at week 6, hemodynamically significant stenosis in the treatment zone was present in 55% of placebo patients and 26% of vonapanitase patients (P = .02). Vonapanitase treatment can also cause arterial and venous dilation through lysis of elastic fibers that normally constrain vessel diameter.[16,17] Finally, in experimental models in animals, fragmentation of elastin is an early and essential component of vascular remodeling that is necessary for AVF maturation.[18] Application of vonapanitase, an elastase, to the AVF immediately after creation could accelerate vascular remodeling that could promote AVF maturation. The previously published data showed that vonapanitase significantly increased the proportion of patients with a mature AVF by ultrasound criteria within 6 to 12 weeks.[10]

Ultrasound-defined maturation in a good predictor of successful AVF use for hemodialysis.[19] Approximately 70% of the patients were on hemodialysis at some time during the study. In this subgroup, approximately half had unassisted use of the AVF for hemodialysis, and an additional 20% had assisted use of the AVF for hemodialysis. AVF use for hemodialysis was defined as use of the trial AVF for hemodialysis for ≥3 months. If hemodialysis was not initiated at least 3 months before the last visit, successful use was defined as use for at least 1 month and in use at the patient's last study visit. This definition was chosen because the majority of investigators were surgeons who did not have access to dialysis blood flow data. This definition is practical as this duration of use is significant and a poorly functioning AVF would not be tolerated over such a time frame. There were no significant differences between treatment groups for either successful unassisted or any use for hemodialysis. In the subset with radiocephalic AVF, there was a trend for more successful use of the fistula in the 30-μg group. This was also the group in which vonapanitase was associated with the greatest increase in AVF maturation.[10]

CONCLUSIONS

In this study, vonapanitase did not significantly improve primary patency in the overall analysis but did significantly improve primary patency for vonapanitase overall and 30 μg in an analysis that excluded patency loss due to cephalic arch and central vein balloon angioplasty. In radiocephalic patients, vonapanitase overall and 30 μg significantly improved primary and secondary patency and reduced the rate of procedures to restore or to maintain patency. Phase 3 confirmatory trials (NCT02110901 and NCT02414841) are under way in patients undergoing creation of radiocephalic AVFs.

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AUTHOR CONTRIBUTIONS

Conception and design: EP, BD, SB
Analysis and interpretation: EP, BD, SB
Data collection: EP, TO, BJ, BD, ASS, SJ, ADS
Writing the article: SB
Critical revision of the article: EP, TO, BJ, BD, ASS, SJ, ADS
Final approval of the article: EP, TO, BJ, BD, ASS, SJ, ADS, SB
Statistical analysis: SB
Obtained funding: SB
Overall responsibility: SB

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