IN.PACT AV Access

Randomized Study of IN.PACT™ AV Access Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon vs. Standard PTA for the Treatment of Obstructive Lesions in the Native Arteriovenous Dialysis Fistulae (AVF)

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Statistical Analysis Plan

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted]
2.0	Following the FDA's recommendations in the IDE approval letter (G160242) on December 14, 2016, the following changes are implemented: • Changed the statement of "two-sided Chi-square test at α=0.05" to "one-sided Z-test at α=0.025" for primary efficacy endpoint per FDA recommendation to be consistent with the alternative hypothesis • Added worst case analysis per FDA recommendation to assess the sensitivity of the primary endpoints • Explicitly expressed the hypotheses of key secondary endpoints in mathematical form per FDA recommendation • Clearly distinguished the "secondary analysis" and "sensitivity analysis" per FDA recommendation. Specified the additional analysis on primary endpoints, including time-to-event analysis, analysis on as-treated subjects and per-protocol subjects. The sensitivity analysis, including multiple imputation, Tipping Point and Worst Case analysis were added. • Added "As-Treated Analysis Set" and "Per-Protocol Analysis Set" and reworded the "as-treated analysis" and "per-protocol analysis" by applying pre-defined analysis set for clarification. • Changed the test method of evaluating the primary safety endpoint from Z-test to Farrington-Manning test per FDA recommendation. The exact test provides a stronger control on type I error for the small event rates. Addition analysis details are added: • Changed the cutoff day for the 6 month target lesion primary patency from 180 days to 210 days. The Target lesion primary patency is a composite endpoint that has two component events- a clinical endpoint of CD-TLR and an imaging based endpoint of thrombosis, using upper limit of clinical visit window (180+30 days) helps to maximize the assessment of imaging data. • Replaced the KD-QOL analysis with the EQ-5D analysis to accommodate CIP update.	[redacted]
3.0	• The poolability assessment for geography is updated to include US vs OUS (Japan and NZ combined).	[redacted]

Version	Summary of Changes	Author(s)/Title
	• Updated the time frame for procedural success from 7 days to 2 days post index procedure. • Updated the blinding plan; CEC and Core lab will remain blinded until the end of the study. • Changed the standard error calculation method from Greenwood to Peto. • Updated the primary and secondary endpoint analysis specification.	
4.0	• Update the incomplete date imputation section. • Format update using the latest SAP template.	[redacted]
5.0	• Extend the study period to 60 months according to the CIP v3.0, with long term endpoints up to 60-months added.	
6.0	• Update according to CIP v4.0, all planned assessment will be up to 36 months, except vital status information will be collected and reported up to 60 months o Updated title to align with CIP v4.0 in Section 3. o Update secondary endpoint descriptions per CIP v4.0 in section 4.2., and 7.9.3.. o Updated section references in Section 7.1.3. o Remove duplicate statement in section 7.5. o Correct typo in section 7.9.1. o Updated section 7.12 to briefly describe changes in planned analyses	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AVF	Arteriovenous "Dialysis" Fistula
CD-TLR	Clinically Driven Target Lesion Revascularization
CEC	Clinical Events Committee
CRF	Case Report Form
DCB	Drug Coated Balloon
ITT	Intent-to-Treat
EQ-5D	EuroQol five dimensions questionnaire
MAR	Missing At Random
PP	Per Protocol
PT	Preferred Term
PTA	Percutaneous Transluminal Angioplasty
SADE	Serious Adverse Device Effect
SAS	Statistical Analysis Software
SAE	Serious Adverse Event
SOC	System Organ Class
TLR	Target Lesion Revascularization

3. Introduction

This document outlines the detailed statistical methods to be implemented for the data collected within the scope of "IN.PACT™ AV Access Study" - Randomized Study of IN.PACT™ AV Access Paclitaxel-Coated Percutaneous Transluminal Angioplasty (PTA) Balloon vs. Standard PTA for the Treatment of Obstructive Lesions in the Native Arteriovenous Dialysis Fistulae (AVF) . The purpose of this plan is to provide a framework within which answers to the study objectives can be achieved in a statistically rigorous fashion, without bias or analytical deficiencies.

Specifically, the plan has the following purpose: To prospectively (a priori) outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of bio-statistical analysis in the medical device industry. Results obtained from the analyses outlined in this document will be the basis of the clinical study report for this study.

4. Study Objectives

To evaluate the safety and efficacy of the IN.PACT AV Access Paclitaxel- coated PTA Balloon Catheter (IN.PACT AV Access Drug Coated Balloon (DCB)) compared to percutaneous transluminal angioplasty (PTA) for treatment of subjects presenting with obstructive lesions of native arteriovenous dialysis fistulae (AVF) in the upper extremity.

4.1 Primary Endpoints

Primary endpoints for the study are as follows:

Primary Efficacy Endpoint: Target Lesion Primary Patency Rate through 6 Months Post-procedure

Defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or access circuit thrombosis measured through 6 months post-procedure.

Primary Safety Endpoint: Serious Adverse Event Rate within 30 Days Post-procedure

Defined as the Serious Adverse Event (SAE) rate involving the AV access circuit through 30 days post-procedure.

4.2 Secondary Endpoints

Secondary endpoints for the study are as follows:

Access Circuit Primary Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure

Defined as freedom from re-intervention in the access circuit or access circuit thrombosis through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

Target Lesion Primary Patency through 3 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure

Defined as freedom from CD-TLR or access thrombosis through 3 Months, 9 Months, 12 Months, 18 Months, and 24 Months post-procedure.

Cumulative Target Lesion Revascularizations Measured through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure

Defined as proportion of subjects with TLR through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

Number of Interventions Required to Maintain Target Lesion Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure

Defined as number of TLR through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

Number of Interventions Required to Maintain Access Circuit Patency through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure

Defined as number of reinterventions in the target lesion and/or access circuit through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

Cumulative Access Circuit Thromboses Measured through 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure

Defined as proportion of subjects with access circuit thrombosis through 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

Device, Procedure, and Clinical Success

Device Success: Defined as successful delivery, inflation, deflation and retrieval of the intact study balloon device without burst at or below rated burst pressure (RBP) at index procedure

Procedural Success: defined at maintenance of patency (≤30% residual stenosis) in the absence of peri-procedural serious adverse device effect (SADE)

Clinical Success: defined as resumption of successful dialysis for at least one session after index procedure

Rate of Device and Procedure Related Adverse Events Reported through 30 Days, 3 Months, 6 Months, 9 Months, 12 Months, 18 Months, and 24 Months Post-procedure.

Device related adverse event rate: defined as proportion of subjects with device related Adverse Events reported through 30 days, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure.

Procedure related adverse event rate: defined as proportion of subjects with procedure related Adverse Events reported post-index procedure until the first successful dialysis session.

The following endpoints will be assessed annually up to 36 months in addition to the assessment through 24 months where applicable:

Target Lesion Revascularizations

Defined as proportion of subjects with TLR up to 36 months post-index procedure

Clinically-Driven Target Lesion Revascularizations

Defined as proportion of subjects with CD-TLR up to 36 months post index procedure

Re-interventions in the access circuit

Defined as proportion of subjects with reinterventions occurring within the access circuit up to 36 months post-index procedure

Abandonment of Target AVF

Defined as proportion of subjects with abandonment of the target AV up to 36 months post-index procedure

Serious Adverse Events

Defined as the Serious Adverse Event (SAE) rate up to 36 months post-index procedure.

Vital Status

Vital status will be collected annually through 60 months for all current subjects. Vital status will be requested for any subjects who have exited the study in the US. As for the subjects in Japan and New Zealand, once a subject exits the study, no medical information can be retrieved. Time-to- event analysis in survival /death will be evaluated according to the Kaplan-Meier method up to 60 months

5. Investigation Plan

This is a prospective, global, multicenter, single-blinded, randomized (1:1) clinical study evaluating the IN.PACT AV Access DCB (study arm) vs. standard PTA (control arm) for the treatment of de novo or non-stented restenotic obstructive lesions up to 100 mm in length in the arteriovenous dialysis fistulae. All eligible subjects who provide informed consent and meet all inclusion/exclusion criteria will be randomized 1:1 based upon lesion type (de novo, restenotic) to the control or study arm. Total enrollment will be 330 subjects at up to 30 global sites, with a minimum of 50% (165) of subjects coming from the U.S. sites, and a minimum of 30% (99) of subjects coming from the Japan sites. There is no minimum enrollment requirement at each site; however, individual sites may enroll no more than 20% of the total study subjects. Approximately 165 study devices will be used in this study.

5.1 Blinding

The study subjects will remain blinded through completion of the 6-month primary efficacy endpoint, including completion of all associated evaluations. Independent Core Laboratories and the Clinical Events Committee (CEC) will remain blinded until the end of the study.

Study site staff (physicians, research coordinators, catheterization lab staff, and other research staff) will not be blinded to treatment assignment due to the macroscopic visual differences between the investigational device and the control device. As study investigators are not blinded to the subject's treatment assignment, no procedures to break the blind in the case of an emergency are required.

Medtronic representatives whose responsibilities require knowledge of treatment assignment to perform their respective roles will not be blinded. Designated individuals within the IN.PACT AV Access study team, Data Solutions, Safety, Customer Service (responsible for device shipment and accountability), and Regulatory will not be blinded. Clinical Customer Service, a small group of individuals who will be responsible for device shipment and reconciliation, will be unblinded, as will the team of monitors assigned to the study.

Unblinded individuals within Medtronic and at the study sites will receive guidance on preserving the blind as required.

The details of binding plan can be found in the *Randomization and Blinding Plan*.

5.2 Duration

Once enrolled, subjects will remain in the study through completion of the required follow-up duration unless the subject withdraws consent, the investigator withdraws the subject, or Medtronic terminates the study for any reason. The enrollment phase is expected to take 15 months. The follow-up duration for each subject is up to 60 months. The total expected duration of the study is approximately 6 years.

The primary safety endpoint will be evaluated 30 days post-procedure; the primary efficacy endpoint will be evaluated 6 months post-procedure. The schedule of events can be found in Section 10.1 of the clinical investigation plan (APV-IN.PACT AV Access).

6. Determination of Sample Size

There are two primary hypotheses for the study. One is for the primary efficacy endpoint – target lesion primary patency through 6 months, and one is for the primary safety endpoint – SAE rate involving the AV access circuit through 30 days post-procedure.

For the primary efficacy endpoint– target lesion primary patency through 6 months, the treatment (p_T) and control (p_C) groups will be compared in a superiority format under the following hypothesis.

$$H_0: \ p_T \leq p_C$$

$$H_A: \ p_T > p_C$$

For the primary safety endpoint- SAE rate involving the AV access circuit through 30 days, the treatment (π_T) and control (π_C) groups will be compared in a non-inferiority format under the following hypothesis.

$$H_0: \ \pi_T \geq \pi_C + 0.075$$

$$H_A: \ \pi_T < \pi_C + 0.075$$

For primary efficacy endpoint of 6-month Target Lesion Primary Patency, with one-sided alpha of 0.025 and assuming 60% primary patency rate in treatment and 40% in control, a one-sided Z-test of proportions will provide at least 92% statistical power to test for superiority, when the effective sample size is 140 in each arm. After accounting for 15% of attrition rate at 6 months, the total sample size will be 330.

For primary safety endpoint through 30-day, an effective sample size of 161 in each arm provides at least 80% power using a Farrington-Manning test based on a one-sided alpha of 0.025, with the assumed event rate of 5% in each arm and a non-inferiority margin of 7.5%. After accounting for 2% of attrition at 30-day follow-up, the total sample size will be 330.

According to above the consideration of both primary endpoints, the total sample size is therefore 330. The power and sample size calculations were performed by using PASS v14.0.7 (NCSS LLC, Kaysville, Utah).The establishment of the assumptions for endpoint rates was based upon publicly available information from currently marketed devices and the literature.

Device Name	Source (SSED, Literature)	Patency Definition	Results
IN.PACT DCB, PTA	NCT01174472 Kitrou, P. M., et al. (2015). Eur J Radiol 84(3): 418-423. Katsanos, K., et al. (2012). J Endovasc Ther 19(2): 263-272.	Angiographic visualization of a lesion with <50% restenosis and no need for any additional repeat interventional procedure within the previously treated lesion, due to failing access.	70% [50%, 90%] in DCB vs 25% [6%, 44%] in PTA
IN.PACT DCB	Patanè D et al. (2014). J Vasc Access 15(5):338-43	The absence of dysfunction of the vascular access, patent lesion or residual stenosis <30% and no need for further reintervention of the TL;	92.3% [82%, 100%] in DCB
GORE VIABAHN Endoprosthesis, PTA	Vesely, REVISE Clinical Trial presented at Scientific Meeting, 2014. SSED	Time interval of uninterrupted patency from initial study treatment to the next access thrombosis or intervention performed on the target lesion.	52.9% [43.8%, 61.6%] in stent graft vs 35.5% [27.4%, 43.6%] in PTA
FLAIR Endovascular Stent Graft, PTA	Haskal et. al. NEJM 362, 6, 494-503, 2010. SSED	Patency (open to blood flow) after the study index procedure until reintervention in the treatment area (within 5 mm proximal or 5 mm distal to the study device or index balloon angioplasty treated area), or thrombotic occlusion that involved the treatment area.	KM rate: 50.6%[40.0%, 60.8%] in stent graft vs 23.3% [14.3%, 32.2%] in PTA
Bard Fluency Stent Graft, PTA	Dolmatch et. al. J Vasc Interv Radiology, 23, 4, 479-487, 2012. SSED	Interval after the index intervention until the next re-intervention at the original treatment site or until the extremity (access) is abandoned for permanent access	KM rate: 65.2%[55.6%, 74.9%] in stent graft vs 10.4% [4.3%, 16.6%] in PTA

Device Name	Source	Primary Safety Endpoint	Results
Bard Fluency Stent Graft	Dolmatch et. al. J Vasc Interv Radiology, 23, 4, 479-487, 2012. SSED	Freedom through 30 days from any localized or systemic adverse events, which reasonably suggests the involvement of the AV access circuit (not including stenosis or thrombosis) that require or result in any of the following alone or in	96.6% (114/118) in stent graft vs 96.8% (122/126) in PTA group

Device Name	Source	Primary Safety Endpoint	Results
		combination: additional interventions (including surgery); inpatient hospitalization or prolongation of an existing hospitalization; or death.	
FLAIR Endovascular Stent Graft, PTA*	Haskal et. al. NEJM 362, 6, 494-503, 2010. SSED	Incidence of adverse events at 6 months	No significant difference in two arms, except for restenosis which was higher in control PTA group
GORE VIABAHN Endoprosthesis, PTA	Vesely, REVISE Clinical Trial presented at Scientific Meeting, 2014. SSED	Freedom from major device-, procedure-, and treatment site-related adverse events through 30 days post-procedure	0% in stent graft group vs 1.4% in the PTA group

*The key adverse events reported include death (5%), CVA (2%), CHF (4%), edema of arm/hand (3%), vessel rupture (3%), and pseudoaneurysm (5%) in the stent graft arm at 6 months

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The number and percentage of subjects enrolled, randomized, completed visit at each scheduled clinical follow-up visit will be summarized by treatment. The number and percentage of subjects who complete the study and who terminate early will be summarized by treatment and by terminate/exit reasons as documented on the case report form (CRF).

7.1.2 Clinical Investigation Plan (CIP) Deviations

A deviation is any event in which the study is not conducted according to the CIP, applicable laws or regulations or the Investigator Agreement. Deviations may include, but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain IRB/EC approval before the start of enrolling subjects in the study
- Included subject did not meet inclusion/exclusion criteria
- Required testing and/or measurements not done or incorrectly done
- Subject did not attend follow-up visit
- Follow-up visit was completed outside window
- Unauthorized use of IN.PACT™ AV Access DCB(s)

- Adverse events/UADE or device deficiencies not reported in the required timeframe by country regulation or as specified in the CIP
- Control of study devices not maintained
- Source data permanently lost
- Enrollment of subjects during lapse of IRB/EC approval
- Enrollment limits exceeded

Counts of deviations, number and percentage of patients who have CIP deviations will be summarized by treatment and by associated visit and reason as documented in the CRF.

7.1.3 Analysis Sets

Primary Analysis Set

Intent-to-treat (ITT) Analysis Set

All primary analyses will be performed using Intent-to-treat (ITT) Analysis Set which includes all randomized subjects. The ITT subjects will be analysed according to their randomized group assignment irrespective of the treatment actually delivered and subject follow-up time, and all events post-randomization will be counted toward study endpoints. In general, all analysis will be performed on evaluable subjects in ITT analysis set. For baseline and treatment characteristics, evaluable subjects refer to subjects who had available data (not missing and not unknown). For clinical outcomes, evaluable subjects refer to subjects who had the event and/or had sufficient follow up for the time point of interest. The details of determining the evaluable subjects for primary and secondary endpoints can be found in section 7.9.1 and 7.9.3.

Secondary Analysis Set

As Treated Analysis Set

As treated analysis set include randomized subjects who received a DCB or PTA. The as treated subjects will be analyzed according to the device they actually received. If the as treated analysis set is different from ITT analysis set, the primary and secondary endpoints will be analyzed on as treated analysis set to assess the sensitivity.

Per-Protocol Analysis Set

Per-Protocol Analysis set include subjects who have: (a) received the randomized treatment as assigned without provisional stenting or other potential bailout procedure; (b) no pre-specified inclusion/exclusion violation(s); and (c) available endpoint data post-index procedure. The pre-specified inclusion/exclusion violations include:

INC 3: Patient has a native AV fistula created ≥ 60 days prior to the index procedure

INC 4: The target AV fistula has undergone successful dialysis for at least 8 of 12 sessions during a four week period

INC 5: Patient has a de novo and/or non-stented restenotic lesion located between the arteriovenous anastomosis and axillosubclavian junction with ≥50% stenosis

INC 6: Patient has a target lesion or a tandem lesion that is ≤ 100 mm in length (by visual estimate)

INC 7: Patient has a target vessel diameter of 4.0 – 12.0 mm (by visual estimate)

INC 8: Patient underwent successful crossing of the target lesion with the guide wire and pre-dilatation with a high pressure PTA balloon defined as:

- Residual stenosis of ≤ 30% AND
- Absence of a flow limiting dissection (Grade ≥C) or perforation

EXC 4: Patient has undergone prior intervention of access site within 30 days of index procedure

EXC 6: Patient has an infected AV access or systemic infection

EXC 8: Patient with secondary non-target lesion requiring treatment within 30 days post index procedure

EXC 9: Patient with hemodynamically significant central venous stenoses that cannot be successfully treated prior to treatment of the target lesion

EXC 10: Patient with target AVF or access circuit which previously had or currently has a thrombosis

EXC 12: Patient with target lesion located central to the axillosubclavian junction

EXC 13: Patient has significant arterial inflow lesion requiring treatment more than 2 cm upstream from the anastomosis in the AV access

EXC 14: Patient has presence of pseudoaneurysm or aneurysm requiring treatment at the lesion site

EXC 15: Patient has presence of a stent located in the target AV access circuit

EXC 19: Patient with clinically significant Steal Syndrome requiring treatment

Per-Protocol Analysis set will be applied to primary and key secondary endpoint analyses.

7.2 General Methodology

Subject data listings and tabular and graphical presentations of results will be provided. Descriptive statistics of continuous variables will be presented by treatment arm and include sample size, mean, median, standard deviation, minimum and maximum. For categorical variables, the number and percentage of subjects in each category will be presented by treatment arm. In general, number of subjects with missing data can be identified from the difference between number of ITT subjects and number of observations.

Unless otherwise specified, dichotomous variables will be evaluated using Fisher's exact tests. Categorical variables will be evaluated by Cochran-Mantel-Haenszel (CMH) Modified

Ridit Scores, i.e. CMH of general association for nominal variables and CMH of row mean score for ordinal variables. Continuous variables will be evaluated by two-sample t-test.

Time to event analysis will be carried out using the Kaplan-Meier method along with Peto standard error. If a subject does not have an event, the time point when a subject becomes un-evaluable will be considered as the censoring time for this subject.

Unless otherwise specified in the table specifications, similar reporting rules will be used for long term endpoints.

7.3 Center Pooling

Poolability of subjects across clinical sites for the primary efficacy and primary safety endpoints analyses will be tested using Cox proportional hazards regression. The Cox model will include the treatment, site, and the treatment-by-site interaction effect as independent variables; if the interaction effect is not statistically significant (defined as $p>0.15$ on the interaction test) or the interaction effect is significant but not qualitative in nature, all data irrespective of site will be analysed as a single analysis cohort. It may be necessary to combine two or more low enrolling study sites into pseudo-sites to allow these analyses. Sites with fewer than 10 subjects will be ranked by enrollment from low to high, then starting from the lowest enrollment site, sites will be combined into a pseudo site until the combined size reaches the median enrollment among all sites. This process will be repeated until all resulting sites have enrollment equal to or greater than 10 subjects. This will be done in a manner to preserve the structure of the study and prevent bias.

Similar poolability analyses will be conducted to assess treatment-by-geography (US vs. Japan vs. New Zealand, and US vs OUS) interaction and treatment-by-lesion status (de novo vs. restenotic) interaction.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

In general, imputation of missing data will not be performed for descriptive statistics. For primary efficacy and primary safety endpoints, subjects who dropped out early and became unevaluable for the primary analysis will be imputed in several ways to access the sensitivity, including multiple imputation and tipping point analysis. The imputation details are described in section 7.9.2.

For incomplete date, unless otherwise specified, the following rules shall be applied in raw data at the database level:

Imputed dates will be limited to date of birth, AE start date and medication start and end dates: date of birth and AE date use worst case rule, medication dates, date of AVF creation and hemodialysis date use less far from correct date rule. Specifically:

- If a date needed for calculation (e.g. date of birth for age) is an incomplete date (e.g. **112006 or ****2006) it will be completed as follows:

- For incomplete event dates or date of birth, '01' or '0101' will be entered, respectively (worst case). However, if an imputed event date is before date of procedure, the date of event will be set equal to the date of procedure.
- For all other incomplete dates '15' or '0715' will be entered, respectively (less far from correct date). In addition, if the missing month is known to be between January and June, the mid-month between the last known month and June may be used; if the missing month is known to be between July and December, the mid-month between the last known month and December may be used. For example, if the last known visit is in July, month September may be used.

If the entire start date of an event or a medication is missing the procedure date will be imputed.

7.5 Adjustments for Multiple Comparisons

To control the overall Type I error (one-sided P=0.025 superiority and one-sided P=0.025 non-inferiority) the following fixed sequence testing procedure will be taken:

Primary efficacy superiority; if significant at one-sided alpha=0.025 and

Primary safety non-inferiority; if significant at one-sided alpha=0.025,

then proceed to key secondary endpoints:

(1) Cumulative target lesion revascularizations (TLR) measured through 6 months post-procedure;

H_0: $t_T \geq t_C$

H_A: $t_T < t_C$

t_x refer to the expected cumulative TLR rate through 6 month (x=T for DCB x=C for PTA). One-sided Z-test will be performed at a significance level of 0.025.

(2) Number of interventions required to maintain target lesion patency through 6 months post-procedure;

H_0: $l_T \geq l_C$

H_A: $l_T < l_C$

l_x refer to the expected number of interventions to maintain target lesion patency through 6 months(x=T for DCB x=C for PTA). The comparison will be performed at one-sided significance level of 0.025 using Wilcoxon Rank Sum Test.

(3) Number of interventions required to maintain access circuit patency through 6 months post-procedure

H_0: $c_T \geq c_C$

H_A: $c_T < c_C$

c_x refer to the expected number of interventions to maintain access circuit patency through 6 months(x=T for DCB x=C for PTA). The comparison will be performed at one-sided significance level of 0.025 using Wilcoxon Rank Sum Test.

(4) Access circuit primary patency through 6 months post-procedure;

H_0: $a_T \leq a_C$

H_A: $a_T > a_C$

a_x refer to the expected access circuit primary patency rate through 6 month (x=T for DCB x=C for PTA). One-sided Z-test will be performed at a significance level of 0.025.

If (1) – (4) all pass the test, the superiority test of primary safety endpoint will be performed

H_0: $\pi_T \geq \pi_C$

H_A: $\pi_T < \pi_C$

π_x refer to the expected event rate of primary safety endpoint at 30-day (x=T for DCB x=C for PTA). Exact test will be performed to compare DCB and PTA.

The testing procedure will stop at the first rejection failure. This sequential approach keeps the family-wise error rate across the primary and key secondary endpoints.

7.6 Demographic and Other Baseline Characteristics

Demographic (age, gender, race, ethnicity and country of enrollment), baseline vital signs, medical history, previous revascularization in AVF, substance use/smoking history, target AVF characteristics, target lesion characteristics, baseline angiography and other clinically relevant baseline variables will be summarized by treatment using general methodology as described in section 7.2.

7.7 Treatment Characteristics

Pre-dilatation, index procedure and post-dilatation procedural characteristics and results, concomitant medical therapy and procedural angiography will be summarized by treatment using general methodology as described in section 7.2.

7.8 Interim Analyses

There are no interim analyses planned for this study.

7.9 Evaluation of Objectives

7.9.1 Primary Analysis of Primary Endpoints

Primary Efficacy Endpoint

Primary efficacy endpoint is defined as freedom from clinically-driven target lesion revascularization (CD-TLR) or access circuit thrombosis measured through 6 months post-procedure. The composite outcome can be derived as follows:

Freedom from CD-TLR	Freedom from Access Thrombosis	6-Month Target Lesion Primary Patency
Yes	Yes	Yes
Yes	No	No
Yes	Missing Data	Missing Data
No	Yes	No
No	No	No
No	Missing Data	No
Missing Data	Yes	Missing Data
Missing Data	No	No
Missing Data	Missing Data	Missing Data

The null and alternative hypotheses for primary efficacy endpoint are:

H_0: $p_T \leq p_C$

H_A: $p_T > p_C$

where p_T and p_C respectively refer to the patency rate through 6 months in treatment and control group.

The count and percentage of subjects with primary patency through 6 months will be presented by treatment arm. The percentages will be computed as

$\hat{p}_i = 1 - \frac{n_i}{m_i}, i = T(treatment), C(control).$

n_i is the number of subjects in each treatment arm who experienced patency-related event (i.e., CD-TLR or access circuit thrombosis, both events will use independent CEC adjudicated results) within 210 days post procedure, m_i is the number of subjects in each treatment arm who experienced patency-related event within 210 days, or had no patency-related event but followed up for at least 150 days. If a subject had no CD-TLR or thrombosis event within 210 days and abandoned AV access circuit within 150 days, the subject will be excluded from the denominator (m_i).

The hypothesis will be tested using Z-test, and the differences between treatments together with a two-sided 95% confidence interval will be calculated.

Primary Safety Endpoint

The null and alternative hypotheses for primary safety endpoint are:

H_0: $\pi_T \geq \pi_C + 0.075$

H_A: $\pi_T < \pi_C + 0.075$

where π_T and π_C respectively refer to the AV access circuit-related SAE rate through 30 days in treatment and control group.

The count and percentage of subjects with AV access circuit-related SAE through 30 days will be presented by treatment arm. The percentages will be computed as

$\hat{\pi}_i = \frac{n_i}{m_i}$,

$i = T, C$.. n_i is the number of subjects in each treatment arm who experienced an AV access circuit-related SAE within 30 days post procedure, m_i is the number of subjects in each treatment arm who experienced an AV access circuit-related SAE event within 30 days or had no AV access circuit-related SAE but followed up for at least 23 days. All AV access circuit-related SAEs will use independent CEC adjudicated results.

Non-inferiority on the safety endpoint will be tested using the Farrington Manning method. The differences between treatments together with the one-sided 97.5% upper confidence limit will be calculated.

To control the overall Type I error the study will be deemed success only if both primary efficacy and primary safety endpoints passed the hypothesis testing.

7.9.2 Additional Analysis of Primary Endpoints

Survival Analysis

Time to target lesion primary patency and AV-access-circuit-related SAE endpoints will be evaluated according to the Kaplan-Meier method. The median time to target lesion primary patency and to AV-access-circuit-related SAE will be presented by treatment. Log-rank tests will be applied to compare the treatment arms.

Survival curves (for primary patency) / cumulative incidence curves (for primary safety) will be provided by treatment. For each time interval as appropriate, the number of subjects at risk at the beginning of the interval, the number of subjects censored in between, and the survival/cumulative incidence rate through the end of interval along with the Peto standard error will be presented for each treatment arm.

Sensitivity analysis for primary endpoints will include the following:

Multiple Imputation will be conducted for primary efficacy endpoint. Tipping point analysis and worse case analysis will be conducted for both primary efficacy and primary safety endpoints.

Multiple Imputation

ITT subjects with missing data for primary efficacy endpoint will be imputed using multiple imputation procedure. The imputation will be carried out in PROC MI in SAS under the missing at random (MAR) assumption. The factors/covariates in the imputation model based on the logistic regression will include treatment group, geographic region (US, Japan and New Zealand), lesion type (De Novo vs Stenotic), age, gender, AVF type, history of CAD and history of PAD. Missing baseline variables will be imputed using PROC MI with 1 imputed data set. 10 imputed data sets will be generated with the treatment effect being assessed in each imputed data. The CD-TLR and access circuit thrombosis will be imputed separately and

composite efficacy endpoint will be derived by mapping the imputed datasets using imputation index. A final single assessment of treatment arm difference will be obtained from combining the results across the imputed datasets, using PROC MIANALYZE in SAS.

Tipping Point Analysis

The number of successes or failures amongst missing data necessary to reject/accept the primary endpoint hypotheses will be determined. Same approach will be used for primary efficacy and primary safety endpoints. Take the primary efficacy endpoint as an example, the following steps will be followed:
If the primary analysis based on available data rejected the null hypothesis,

1. Impute all the missing records in treatment group as failure and all missing records in control group as success, perform the hypothesis testing, stop if null hypothesis is rejected; otherwise continue to step 2;

2. Change one record in treatment group to success and one record in control group to failure, perform the hypothesis testing, stop if rejected; otherwise repeat step 2 until the first time of rejection.

If the primary analysis based on available data failed to rejected the null hypothesis,

1. Impute all the missing records in treatment group as success and all missing records in control group as failure, perform the hypothesis testing, stop if fail to reject null hypothesis; otherwise continue to step 2;

2. Change one record in treatment group to failure and one record in control group to success, perform the hypothesis testing, stop if fail to reject; otherwise repeat step 2 until the first time of rejection failure.

Worst case analysis

All missing endpoint in the treatment arm will be imputed as failures and all missing endpoint in the control arm will be imputed as successes.

The primary endpoints will also be analyzed on Per-Protocol Analysis set, As-Treated Analysis Set and No-Bailout subset to assess sensitivity.

7.9.3 Analysis of Secondary Endpoints

Descriptive statistics for all secondary endpoints will be provided. The clinical outcomes will use independent CEC adjudicated results. The treatment difference and corresponding 95% confidence intervals will be calculated and reported. Survival analysis will be performed for secondary endpoints that are applicable (described below). The critical secondary endpoints will be compared between treatments sequentially in the pre-specified order at section 7.5.

Clinical outcomes considering the first occurrence

- Access Circuit Primary Patency through 30 days, 3, 6, 9, 12, 18, 24 and 36months
- Target Lesion Primary Patency through 30 days, 3, 9, 12, 18, 24 and 36 months

- Target Lesion Revascularization through 30 days, 3, 6, 9, 12, 18, 24, and 36 months
- Access Circuit Thromboses through 30 days, 3, 6, 9, 12, 18, 24 and 36 months
- Clinically-Driven Target Lesion Revascularizations through 6, 12, 24, and 36 months
- Re-interventions in the access circuit through 6, 12, 24, and 36 months
- Abandonment of Target AVF through 6, 12, 24, and 36 months
- Serious Adverse Events involving access circuit through 12, 24, and 36 months
- All-cause death including vital status through 12, 24, 36, 48, and 60 months

The cumulative event rate for these clinical endpoints will be summarized on patient basis by treatment and compared using Chi-square test where applicable.

For abandonment of target AVF, cumulative event rate at each visit based on all subjects in each treatment arm will be summarized.

Unless otherwise specified, events related to the primary and secondary endpoints are based on CEC adjudicated data; for different reporting time points, the correspondent reporting cutoff days will be used. For each visit reporting time point, the event rate will be calculated as the proportion of number of subjects with certain event term over the number of evaluable subjects. The evaluable subjects at each reporting time point include all subjects in the analysis set and

1) Had an event within (on or before) the reporting cutoff days, or
2) Date of last contact is after the lower limit of the reporting window
3) If a subject had no event and abandoned AV Access Circuit on or before the lower limit of reporting window, he/she will be considered not evaluable.

'Days to event' (date of earliest event – date of index procedure) and 'Days to last contact' (date of last contact – date of index procedure) are usually used for the determination of the eligibility of the 'evaluable subject'. *The last contact date will be calculated based on the information gathered from all available dates during the follow-ups.*

The 'Reporting Cutoff Days', 'Lower limit of the Reporting Window' and the correspondent visits are as follows:

Visit	**Lower Limit of the Reporting Window**	**Reporting Cutoff Days**
1-month	23 days post-index procedure	30 days post-index procedure
3-month	75 days post-index procedure	90 days post-index procedure
6-month	150 days post-index procedure	180 days post-index procedure
9-month	240 days post-index procedure	270 days post-index procedure
12-month	330 days post-index procedure	360 days post-index procedure
18-month	510 days post-index procedure	540 days post-index procedure
24-month	690 days post-index procedure	720 days post-index procedure

Visit	Lower Limit of the Reporting Window	Reporting Cutoff Days
36-month	1050 days post-index procedure	1080 days post-index procedure

In particular, for Access circuit primary patency through 6 months, 210 days will be used as the reporting cutoff days when determining the numerator, to align with the primary efficacy endpoint analysis.

Survival analysis will also be performed for these endpoints using Kaplan-Meier method. Survival curve or cumulative incidence curves will be provided by treatment. For each time interval as appropriate, the number of subjects at risk at the beginning of the last day of an interval, the number of subjects censored in between, and the survival/cumulative incidence rate through the end of interval along with the peto standard error and the 95% confidence interval will be presented for each treatment arm. Subjects who experience an event such as loss of TLPP, loss of ACPP, CD-TLR, TLR, reintervention at access circuit, access circuit thrombosis, SAE_AC, etc. post-index procedure as adjudicated by CEC will be counted as an event or failure. Subjects not completing the study will be censored after their last available contact. Results from the Kaplan-Meier estimates will be reported at 30 day, 6, 7, 9, 12, 24, and 36 months for each randomization arm respectively, where applicable, reporting time points may vary depends on the reporting requirement and the available data. Kaplan-Meier estimates and related plot will be reported through 60 months for all-cause mortality including vital status.

Clinical outcomes considering all occurrence

- Number of Interventions Required to Maintain Target Lesion Patency
- Number of Interventions Required to Maintain Access Circuit Patency

The mean, median, standard deviation and range of number of interventions per patient will be presented by treatment at each follow up time point. The comparison will be performed based on Wilcoxon Rank Sum Test.

Device, Procedure, and Clinical Success

Device success will be captured in the procedure CRF and will be analyzed per patient level. If multiple study balloon devices were used on one subject, all devices must achieve success in order to claim the device success for this subject. The number and percentage of subjects who achieved device success will be reported by treatment. The comparison will be performed based on Chi-square test.

Procedural Success will be defined with two components: maintenance of patency (≤30% residual stenosis) and absence of peri-procedural SADE. The final residual stenosis will be based on the core lab data. If there is no core lab reading available, the site reported final stenosis will be used. The peri-procedural SADE is defined as device related serious adverse event occurred at the time of first successful dialysis session or within 2 days post procedure, whichever is first. Procedural Success will be analyzed per patient level. The number and

percentage of subjects who achieved procedural success will be reported by treatment. The comparison will be performed based on Chi-square test.

Clinical Success is defined as resumption of successful dialysis for at least one session after index procedure. Clinical success will be analyzed per patient level. The number and percentage of subjects who achieved Clinical Success will be reported by treatment. The comparison will be performed based on Chi-square test.

Rate of Device and Procedure Related Adverse Events Reported

The number and percentage of subjects who experienced device related adverse events and procedure related adverse events will be summarized by SOC and PT terms and by treatment through 30 days, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months post-procedure. Fisher exact test will be used to test treatment difference.

Key secondary endpoints will also be analyzed on Per-Protocol Analysis set and No-Bailout Analysis set.

7.9.4 Subset Analysis

Additional pre-specified subgroup analyses to assess consistency of treatment differences will be conducted on primary and key secondary endpoints for the following:

- Lesion type (De novo, restenotic lesion)
- AVF Type (Radial Cephalic fistula, Brachial Cephalic, Brachial Basilic Transposition, other)
- Lesion location (Anastomosis, Juxta anastomosis, Venous outflow, Arterial inflow)
- Single and multiple balloon use
- Gender
- Age (≤ Median, > Median)
- Diabetics
- History of Dialysis
- Subjects without provisional stenting or other bailout procedure

Subset analysis based on Race and Ethnicity will be performed if applicable.

Bailout procedures during the index procedure may confound the evaluation of treatment effect. In the AV Access study, provisional stenting should be avoided unless required for subject safety. Only non-drug-coated stents that are approved in country of the study site and for this indication may be used in this study. Given the provisional stent during the index procedure is considered as the most frequently used bail-out approach and its low anticipated incidence, the impact of the bailout procedure will be focused on the provisional stent status and the sub-analysis will be completed to investigate descriptively if the treatment effect in subjects without any bailout procedures is consistent with the effect in all subjects.

There will be no formal hypothesis testing on these subsets due to insufficient power. The primary purpose of this subset analysis is to assess consistency of results across subgroups.

7.9.5 Duplex Ultrasound

Duplex ultrasound outcomes at each scheduled follow up visit (30 day, 6 month and 12 month) will be summarized descriptively by treatment using general methodology as described in section 7.2.

7.10 Safety Evaluation

All Adverse Events (AEs) will be coded using MedDRA dictionary, version 16.1 or newer. All AEs post informed consent will be collected and presented in a listing. The AEs started during or post index procedure through the end of study will be tabulated. The AEs, SAEs, and AEs leading to death, will be summarized by treatment, SOC and PT terms, and by time period. The relationship of AEs to procedure, device and therapy will also be summarized respectively. Fisher exact test will be used to test treatment difference.

Data listing of Serious Adverse Device Effect will be provided if applicable.

7.11 Health Outcomes Analyses

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal.

For each of the five domains, the number of percentage of subjects at each level will be summarized by treatment. The mean of EQ-5D index value and VAS and the mean change from baseline will be summarized by treatment. The treatment comparison at each visit will be performed using analysis of covariance model, which includes change from baseline as the response, treatment and baseline as the dependent variables.

7.12 Changes to Planned Analysis

Planned analysis specified in version 5.0 will no longer be performed once all planned analyses are completed through 36 months follow-up. Only the death with vital status will continue to be reported through 48 and 60 months.

8. Validation Requirements

All analyses will be independently double programmed by SAS Programming team.

9. References

Dolmatch BL, Duch JM, Winder R, et al., "Salvage of angioplasty failures and complications in hemodialysis arteriovenous access using the FLUENCY Plus Stent Graft: technical and 180-day patency results", J Vasc Interv Radiol. 2012; 23: 479–487.

Haskal ZJ, Trerotola S, Dolmatch B, et al., "Stent graft versus balloon angioplasty for failing dialysis-access grafts", N Engl J Med. 2010; 362: 494–503.

Vesely, REVISE Clinical Trial presented at Scientific Meeting, 2014.

Hays, R.D. et. al. (1997). Kidney Disease Quality of Life Short Form (KDQOL-SF™), Version 1.3: A Manual for Use and Scoring. Santa Monica, CA: RAND, P-7994.