Clinical Study – The ELITE Study

Introduction

The safety and effectiveness of the PerQseal Elite VCD was evaluated in the ELITE Study to support the approved indications for use.

Study Design

ELITE was a prospective, multicenter, single-arm study conducted in the EU at 8 clinical centers. The objective of the study was to evaluate the safety and effectiveness of the PerQseal Elite VCD when used to achieve hemostasis of common femoral arteriotomies created by 14 to 22 F sheaths (arteriotomies up to 26 F) in patients undergoing percutaneous catheter-based interventional procedures.

All patients were scheduled for follow-up examinations at 30 minutes, 1 hour, 12-24 hours, 30 days (±7 days), and 180 days (± 30 days) post-PerQseal Elite deployment to monitor the complete bioabsorption of the implant. Follow-up evaluations at scheduled visits included lower extremity pulse assessment, targeted physical exam, ankle brachial index (ABI) of both legs, hemoglobin level, a duplex ultrasound of PerQseal Elite and associated vasculature, and an AE assessment.

Endpoint Definitions

Primary Endpoints
The primary safety endpoint was the rate of major access site complications attributable to the PerQseal Elite device through 30 days, as adjudicated by the Clinical Events Committee (CEC) as study device related.

The primary effectiveness endpoint was the Time to Hemostasis (TTH), defined as the elapsed time in minutes from PerQseal Elite (Introducer-sheath and Delivery Device) removal to first observed cessation of common femoral artery (CFA) bleeding, excluding cutaneous or subcutaneous oozing, and in the absence of a developing hematoma.

Secondary Endpoints
The secondary safety endpoint was the incidence of minor access site complications attributable to the PerQseal Elite device through 30 days, as classified by an independent CEC as study device related.

Five (5) secondary effectiveness endpoints were tested:

- *PerQseal Elite Technical Success Rate*: The number of PerQseal Elite devices that are deployed and achieve hemostasis (i.e., cessation of arterial bleeding excluding cutaneous or subcutaneous oozing) without need for more than 10 minutes of firm, adjunctive manual compression or alternative treatment (other than adjunctive endovascular ballooning) at target access site, divided by the total number of PerQseal devices where deployment was attempted.
- *PerQseal Elite Treatment Success Rate*: The number of subjects who meet PerQseal Elite Technical Success without experiencing a device related Major Access Site Complication (based on CEC adjudication) through 30 days, divided by the total number of subjects where PerQseal Elite device deployment was attempted.
- *Time to Device Deployment (TTDD)*: The time from insertion of the PerQseal Elite delivery device into the PerQseal Elite Introducer sheath to complete removal of the PerQseal Elite (Delivery Device and Introducer-sheath) from the subject following PerQseal Elite deployment.
- *Time to Ambulation*: The elapsed time from PerQseal Elite removal until the subject can walk 20 feet/6 meters without arterial re-bleeding at the target access site. This endpoint was evaluated only for subjects who are ambulatory (e.g., not confined to wheelchair or bed) at the time of enrollment.
- *Total Closure Time*: Time to Hemostasis (TTH) plus Time to Device Deployment (TTDD).

Analysis of Primary Endpoints
For both primary endpoints, a null and alternative hypothesis were tested. Both null hypotheses needed to be rejected for the study to be considered successful. The study was a single-arm study, where the primary safety endpoint and primary effectiveness endpoint were compared to respective performance goals. Performance goals were derived from meta-analyses of major vascular complication rates and time to hemostasis for large hole vascular closure devices from relevant contemporary peer-reviewed medical literature.

In addition, the following outcomes were evaluated:

- *Incidence of Major Vascular Access Site Complications per VARC-3*[1]: Incidence of major vascular access site complications attributable to the PerQseal Elite device through 30 days, based on CEC adjudication, according to VARC-3 definitions.
- *Incidence of Minor Vascular Access Site Complications per VARC-3*: Incidence of minor vascular access site complications attributable to the PerQseal Elite device through 30-days, based on CEC adjudication.

Analysis Populations

The analysis populations are described below:

Table 1: Analysis Populations

Population	Definition	Number
Modified Intent-to-Treat (mITT)	The subset of the ITT population who underwent attempted access site closure with the PerQseal Elite device, excluding subjects who met procedural exclusion criteria, required an unrelated intervention at the access site compromising the implant, or had the device intentionally removed prior to deployment	121 subjects^
Per-Protocol (PP)	mITT subjects with no major protocol deviations who either experienced the primary safety event or completed the 30-day follow-up evaluation	108 subjects
mITT with 30-day follow-up	mITT subjects who completed the 30-day follow-up evaluation	118 subjects
PP with 30-day follow-up	PP subjects with no major protocol deviations who experienced the safety endpoint or completed the 30-day follow-up evaluation	106 subjects
mITT for Primary Effectiveness	mITT subjects for whom Time to Hemostasis (TTH) was measured	113 closures (108 subjects)
PP for Primary Effectiveness	mITT subjects with no major protocol deviations and for whom Time to Hemostasis (TTH) was measured	109 closures (104 subjects)
^There were 5 bilaterial mITT subjects for a total of 126 closures.		

Study Population Baseline Characteristics

The study population in the ELITE study had 121 mITT subjects with an average age of 78.2 ± 7.4 years, with most subjects being male (70.2%) and suffering from prevalent conditions such as hypertension (74.4%), diabetes (24.0%), and antithrombotic medication history (20.7%) (**Table 2** and **Table 3**). No demographic data were required to be collected as part of the ELITE study.

[1] VARC-3 WRITING COMMITTEE; Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, Bax JJ, Leipsic JA, Blanke P, Blackstone EH, Finn MT, Kapadia S, Linke A, Mack MJ, Makkar R, Mehran R, Popma JJ, Reardon M, Rodes-Cabau J, Van Mieghem NM, Webb JG, Cohen DJ, Leon MB. Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. J Am Coll Cardiol. 2021 Jun 1;77(21):2717-2746.

Table 2: Baseline Demographics – mITT Subjects

Characteristic	Mean ± SD (N)	% (n/N)
Age (years)	78.2 ± 7.4 (121)	-
Height (cm)	171.7 ± 8.60 (121)	-
Weight (kg)	80.1 ± 13.5 (121)	-
Male	-	70.2% (85/121)
Female	-	29.8% (36/121)

Table 3: Baseline Medical History – mITT Subjects

Condition	% (n/N)
Hypertension	74.4% (90/121)
Diabetes	24.0% (29/121)
Severe acute non-cardiac systemic disease, autoimmune disease or terminal illness	1.7% (2/121)
Clinically significant peripheral vascular disease	0.8% (1/121)
Claudication or rest pain	0.0% (0/121)
Bleeding diatheses	0.0% (0/121)
Previous peripheral vascular surgery involving the aorta or lower extremities	2.5% (3/121)
Previous amputation of either left or right leg	0.0% (0/121)
Previous arterial access performed using the proposed artery	9.9% (12/121)
Antithrombotic medication history	20.7% (25/121)
Pre-existing nerve injury[a]	0.8% (1/121)
Ambulatory	99.2% (120/121)

[a] One subject was reported with a neck injury unrelated to the ipsilateral treated leg.

Procedural Data

The majority of procedures (72.7%) utilized the right leg for access, with 4.1% (5/121) of subjects undergoing bilateral access. All subjects received local anesthesia at a minimum, with 8.3% (10/121) receiving general anesthesia, 4.1% (5/121) receiving sedation, and the remainder receiving regional blocks. Intraprocedural anticoagulant or antiplatelet therapy was administered to all subjects (100%). Additional metrics including activated clotting time, estimated blood loss during the primary and index closure procedure, and approximate depth of tissue tract are reported in **Table 4**.

Table 4: Procedural Information – mITT Subjects

Activated Clotting Time (ACT [seconds]	
Mean ± SD (N)	181.8 ± 46.08 (121)
Median (Q1, Q3)	178.0 (147.0, 211.0)
Min, Max	90.0, 300.0
Anticoagulant/antiplatelet therapy given during procedure	100.0% (121/121)
Estimated blood loss during the Primary procedure (cc)	
Mean ± SD (N)	43.5 ± 90.58 (121)
Median (Q1, Q3)	10 (0, 40)
Min, Max	0, 500
Estimated blood loss during the Index closure procedure (cc) [1]	
Mean ± SD (N)	23.5 ± 53.79 (125)
Median (Q1, Q3)	0 (0, 20)
Min, Max	0, 400
Approximate depth of tissue tract (mm) [2]	
Mean ± SD (N)	3.8 ± 1.16 (126)
Median (Q1, Q3)	4.0 (3.0, 4.0)
Min, Max	1.0, 8.0

[1] Refers to blood loss during the index closure procedure.

[2] Subjects may have had procedures in both legs. The N is based on the number of procedures, not the number of subjects.

To accurately reflect the size of the arteriotomy closed by the device, **Table 5** details the outer diameter (OD) of the primary procedure sheaths utilized in the study. The outer diameters ranged from 15 to 26 F, which is the clinically relevant metric for large-bore vascular closure.

Table 5: Largest Primary Procedure Sheath Used – mITT by Procedure

Outer Diameter of Largest Sheath Used (F)*	Endovascular Aneurysm Repair (EVAR)	Transcatheter Aortic Repair (TAVR)	Total
15	1	0	1
16	11	8	19
18	6	28	34
19	5	4	9
20	7	9	16
22	0	25	25
23	1	0	1
24	0	18	18
26	0	3	3
Total	**31**	**95**	**126**

*For procedures that used sheathless devices (11), OD size reported by site was the arteriotomy size. One (1) treatment PCI+PTSMA+BAV was classed as TAVR and one (1) treatment Arteria iliac communis aneurysm was classed as EVAR.

Safety Results

Primary Safety Endpoint: Rate of Major Access Site Complications Through 30-Days
The primary safety endpoint was the rate of major access site complications attributable to the device through 30 days, as adjudicated by the CEC.

The primary safety endpoint was successfully met across all mITT and PP analysis populations. The upper bound of the one-sided 97.5% confidence interval for major access site complications associated with the device was well below the pre-specified performance goal for safety of 14.05%. Moreover, all related p-values were below the significance threshold of 0.025 (**Table 6**). Major access site complication rates are further stratified by type of complication in **Table 7**.

Table 6: Major Access Site Complication Rates, Confidence Intervals, and p-values Across Four Analysis Populations

Analysis Population	% (n/N) [97.5% CI]	p-value
mITT with 30-day follow-up*	3.4% (4/118) [0.0%, 8.45%]	< 0.001
PP with 30-day follow-up	0.9% (1/106) [0.0%, 5.14%]	< 0.001
All mITT population	3.3% (4/121) [0.0%, 8.25%]	< 0.001
All PP population	0.9% (1/108) [0.0%, 5.05%]	< 0.001

* Primary analysis | CI, Confidence Interval

Table 7: Major Access Site Complication Rate Stratified by Type of Complication in mITT Population with 30-day follow-up

Major Complication Rates by Study Population	% (n/N)
Access site-related bleeding due to a failure of the PerQseal Elite device that requires transfusion of blood product(s)	0.0% (0/118)
Device related vascular injury that requires surgical repair or percutaneous stent-graft placement	3.4% (4/118)
Any new and sustained (> 24 hrs) device-related ipsilateral lower extremity ischemia, documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram, which causes a threat to the viability of the limb, and/or requires surgical repair or additional percutaneous intervention	0.0% (0/118)
Surgery for device-related nerve injury	0.0% (0/118)
Permanent (lasting to 30-days) device-related nerve injury	0.0% (0/118)
Access site infection requiring intravenous antibiotics, drainage and/or extended hospitalization	0.0% (0/118)

Secondary Safety Endpoint: Rate of Minor Access Site Complications Through 30-Days
The secondary safety endpoint was the incidence of minor access site complications attributable to the PerQseal Elite device through 30-days, as classified by the CEC.

Across all analysis populations, the incidence of minor complications remained well below the pre-specified Clinical Acceptance Criterion (CAC) of 20% (**Table 8**). Minor access site complication rates are further stratified by type of complication in **Table 9.**

Table 8: Minor Access Site Complication Rates Across Four Analysis Populations

Analysis Population	Complication Rate [97.5% CI]	p-value
mITT with 30-day follow-up*	0.8% (1/118) [0.0000, 0.0463]	< 0.001
PP with 30-day follow-up	0.9% (1/106) [0.0000, 0.0514]	< 0.001
All mITT population	0.8% (1/121) [0.0000, 0.0452]	< 0.001
All PP population	0.9% (1/108) [0.0000, 0.0505]	< 0.001
*Primary analysis		

Table 9: Minor Access Site Complication Rate Stratified by Type of Complication in mITT Population with 30-day follow-up

Minor Complication Events by Type	% (n/N)
Non-treated pseudoaneurysm documented by ultrasound	0.0% (0/118)
Pseudoaneurysm treated with ultrasound-guided compression, ultrasound-guided thrombin injection, or ultrasound-guided fibrin adhesive injection	0.8% (1/118)
New non-treated or treated arteriovenous (AV) fistula documented by ultrasound	0.0% (0/118)
Access site hematoma greater than or equal to 10 cm, confirmed by ultrasound	0.0% (0/118)
Late (following hospital discharge) access site-related arterial bleeding	0.0% (0/118)
Ipsilateral lower extremity arterial emboli	0.0% (0/118)
Ipsilateral deep vein thrombosis	0.0% (0/118)
Transient access site-related nerve injury	0.0% (0/118)
Access site infection treated with intramuscular or oral antibiotics	0.0% (0/118)

Exploratory Safety Endpoints: Incidence of Major and Minor VARC-3 Defined Complications
Exploratory safety endpoints were the incidence of major and minor VARC-3 defined complications (**Table 10, Table 11**). The upper bound of the one-sided 97.5% confidence interval for major VARC-3 complications was well below the pre-specified performance goal for primary safety of 14.05%. Moreover, all related p-values were below the significance threshold of 0.025. Additionally, minor VARC-3 complications were below the CAC of 20% in all populations.

Table 10: VARC-3 Major Device-Related Vascular Access Site Complication Rates

Analysis Population	% (n/N) [97.5% CI]	p-value
mITT with 30-day follow-up	0.0% (0/118) [0.0%, 3.08%]	< 0.0001
PP with 30-day follow-up	0.0% (0/106) [0.0%, 3.42%]	< 0.0001

Table 11: VARC-3 Minor Device-Related Vascular Access Site Complication Rates

Analysis Population	% (n/N)
mITT with 30-day follow-up	4.2% (5/118)
PP with 30-day follow-up	1.9% (2/106)

Effectiveness Results

Primary Effectiveness Endpoint: TTH
The primary effectiveness endpoint was time to hemostasis (TTH), defined as the elapsed time in minutes from PerQseal Elite (Introducer-sheath and Delivery-Device) removal to first observed cessation of common femoral artery (CFA) bleeding, excluding cutaneous or subcutaneous oozing, and in the absence of a developing hematoma. The analysis of effectiveness in the study was based on mITT subjects who had TTH recorded at the end of the index procedure.

The upper bound of the confidence intervals for mean TTH was well below the pre-specified performance goal of 19.7 minutes. Moreover, all related p-values were below the significance threshold of 0.025 (**Table 12**).

Table 12: Time to Hemostasis – mITT and PP Populations

Analysis Population	Mean in Mins (SD) [Median]	Upper 97.5% CI in Mins	p-value
mITT with TTH* (N = 113)	0.9 (2.33) [0]	1.36	< 0.001
PP with TTH (N = 109)	0.7 (1.77) [0]	1.08	< 0.0001
*Primary analysis			

Secondary Effectiveness Endpoints
The results of the secondary effectiveness endpoints, including technical success rate, treatment success rate, time to device deployment (TTDD), time to ambulation (TTA), and total closure time (TCT) are provided in Table 13.

Table 13: Secondary Effectiveness Endpoints

Parameter	Value
Technical Success Rate (%, n/N)	88.9% (112/126)
Treatment Success rate (%, n/N)	89.0% (105/118)
TTDD in min (Mean ± SD (N))	2.9 ± 2.83 (113)
Time to Ambulation in hr (Mean ± SD (N))	15.5 ± 10.70 (102)
Total Closure Time in min (Mean ± SD (N))	3.9 ± 3.88 (113)

Clinical Study Conclusion

The ELITE study evaluated the safety and effectiveness of the PerQseal Elite VCD in patients undergoing percutaneous catheter-based interventional procedures requiring large-bore common femoral arterial access. The endpoints were achieved. In addition, no unanticipated adverse device effects (UADEs) or unanticipated serious adverse device effects (USADEs) were reported during the study, and no device-related deaths were reported. The ELITE study provides direct clinical evidence supporting the safety and effectiveness of the PerQseal Elite VCD.

Overall, the data from the ELITE study establishes that the PerQseal Elite device is safe and effective for its intended use.