SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Eluting Coronary Stent System
Device Trade Name:	Svelte SLENDER Sirolimus-Eluting Coronary Stent Integrated Delivery System (SLENDER IDS®) Svelte DIRECT Sirolimus-Eluting Coronary Stent Rapid Exchange Delivery System (DIRECT RX®)
Device Procode:	NIQ
Applicant's Name and Address:	Svelte Medical Systems, Inc. 675 Central Avenue, Suite 2 New Providence, New Jersey 07974 USA
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P210014
Date of FDA Notice of Approval:	December 13, 2021

II. INDICATIONS FOR USE

The Svelte SLENDER Sirolimus-Eluting Coronary Stent Integrated Delivery System (Svelte SLENDER IDS) is indicated for improving coronary artery luminal diameter in patients with symptomatic heart disease due to atherosclerotic lesions ≤ 24 mm in length in native coronary arteries with ≥ 2.25 mm to ≤ 4.00 mm reference vessel diameters, using direct stenting or pre-dilatation interventional techniques.

The Svelte DIRECT Sirolimus-Eluting Coronary Stent Rapid Exchange Delivery System (Svelte DIRECT RX) is indicated for improving coronary artery luminal diameter in patients with symptomatic heart disease due to atherosclerotic lesions ≤ 34 mm in length in native coronary arteries with ≥ 2.25 mm to ≤ 4.00 mm reference vessel diameters, using direct stenting or pre-dilatation interventional techniques.

III. CONTRAINDICATIONS

The Svelte SLENDER IDS and the Svelte DIRECT RX (collectively, Svelte DES) are contraindicated for use in patients:

- Unable to receive anti-platelet and/or anti-coagulant therapy.

- With known hypersensitivity to sirolimus, PEA III Ac Bz, cobalt, chromium, nickel, tungsten or contrast media.
- Judged to have lesions preventing complete inflation of an angioplasty balloon or proper placement of a coronary stent or delivery system, including chronic total occlusions.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Svelte DES labeling.

V. DEVICE DESCRIPTION

The Svelte DES is a combination product consisting of (1) a cobalt chromium (CoCr) alloy stent coated with a bioresorbable polymeric drug carrier containing the anti-proliferative drug sirolimus and (2) the delivery system, either fixed-wire (SLENDER IDS) or rapid exchange (DIRECT RX).

The characteristics of the Svelte DES are described in **Table 1**.

Table 1. Svelte DES Product Characteristics

Characteristic	Svelte DES SLENDER IDS	Svelte DES DIRECT RX
Stent Pattern	3-cell (2.25, 2.50, 2.75, 3.00 mm diameter) 4-cell (3.50, 4.00 mm diameter)	
Stent Lengths (mm)	8, 13, 18, 23, 28	8, 13, 18, 23, 28, 33, 38
Stent Diameters (mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	
Stent Strut Thickness (mm)	2.25 – 3.00 mm diameters: 0.081 mm 3.50 – 4.00 mm diameters: 0.084 mm	
Stent Material	A medical grade L605 CoCr alloy	
Drug Component	A conformal (all surfaces of the stent) coating of a bioresorbable polymer loaded with 213 $\mu g/cm^2$ of sirolimus	
Delivery System Working Length	145 cm	139 cm
Delivery System Design	0.014" fixed-wire catheter with integrated torquer and single access port to inflation lumen	Rapid exchange with a single access port to inflation lumen. Designed for guide wires $\leq$ 0.014"
Stent Delivery System Balloon	Compliant balloon with two radiopaque markers to designate the stent placement on the balloon	
Guiding Catheter Compatibility	$\geq$5 F (min. guide catheter ID of 0.056"/1.42 mm)	
Balloon Inflation Pressure	Nominal: 12 atm (1216 kPa) Rated Burst Pressure: 18 atm (1824 kPa)	
Catheter Shaft Outer Diameter	Distal: 0.029 in (2.2 F, 0.73 mm) Proximal: 0.025 in	Distal: 0.035 in (2.7 F, 0.89 mm) Proximal: 0.026 in

Characteristic	Svelte DES SLENDER IDS	Svelte DES DIRECT RX
	(1.9 F, 0.63 mm)	(2.0 F, 0.67 mm)

A. Device Component Description

The Svelte DES stent is made of CoCr. The stent has two designs that are differentiated by the number of cells and the number of links. The 3-cell design with three links around the circumference is used for 2.25-3.00 mm diameter stents and the 4-cell design with four links around the circumference is used for 3.50-4.00 mm diameter stents. Each stent length configuration has end units that make up the end columns and repeating inner units that make up the internal columns. In order to create various stent lengths, the number of repeating inner columns is varied. **Figure 1** illustrates a 3-cell (top) and 4-cell (bottom) Svelte DES stent.

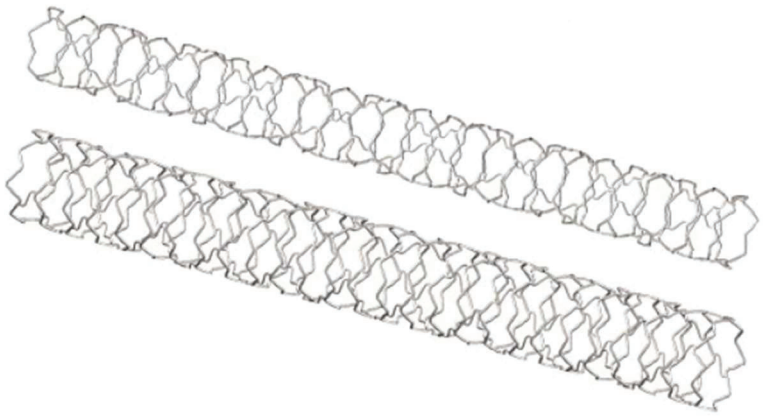

Figure 1: 3-Cell (top) and 4-Cell (bottom) Stent Configurations

The stent is crimped onto the balloon of one of the two available delivery systems: SLENDER IDS or DIRECT RX.

SLENDER IDS is a novel fixed-wire delivery system consisting of a shapeable, radiopaque wire tip, low-compliant delivery balloon and proximal shaft. SLENDER IDS contains two proximal shaft markers (90 cm and 100 cm) indicating the position of SLENDER IDS relative to the end of a brachial or femoral catheter. An integrated torquing device located on the proximal end of the catheter shaft facilitates navigation. The Slender IDS has a very low profile and integrated design that is particularly suited for use with a direct PCI strategy. **Figure 2** provides a pictorial representation of the SLENDER IDS.

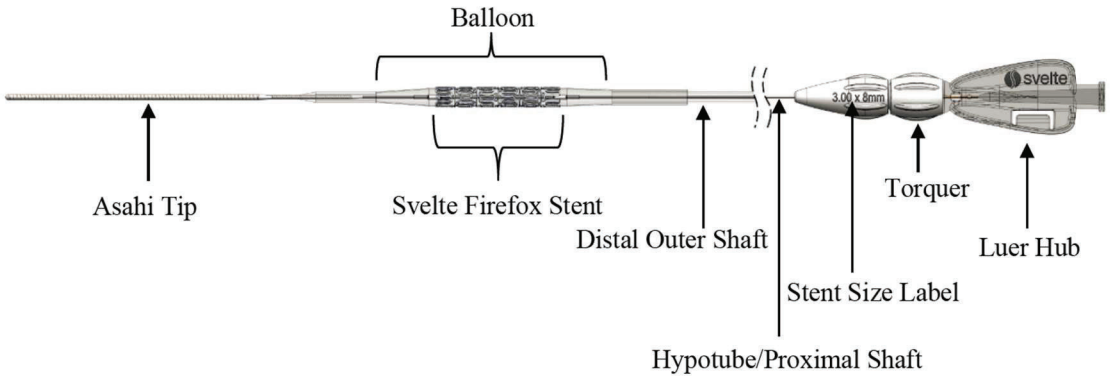

Figure 2: SLENDER IDS Delivery System

DIRECT RX is a rapid exchange delivery system with a low-compliant delivery balloon. **Figure 3** provides a pictorial representation of the DIRECT RX.

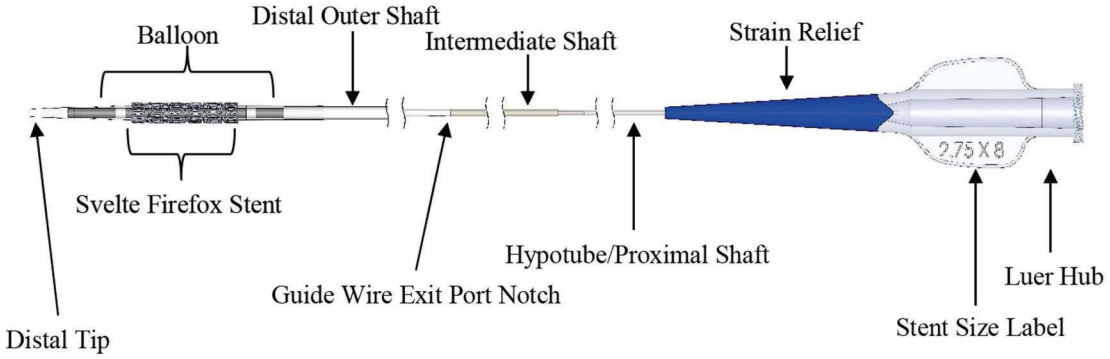

Figure 3: DIRECT RX Delivery System

B. Drug Component Description

The Svelte DES stent is conformally coated with a bioresorbable drug coating. The drug matrix is composed of sirolimus (the active ingredient) and bioresorbable polyesteramide (PEA; inactive ingredient).

1. Sirolimus

Sirolimus (also known as rapamycin) is the active pharmaceutical ingredient in the Svelte family of stents. The sirolimus chemical name is:

[3S[3R*[S*(1R*,3S*,4S*)),6S*,7E,9S*,10S*,12S*,14R*,15E,17E,19E,21R*,23R*,26S*,27S*,34aR*]]-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacontine-1,5,11,28,29(4H,6H,31H)-pentone.

The molecular structure of sirolimus is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.19 Da. The chemical structure is provided in **Figure 4**.

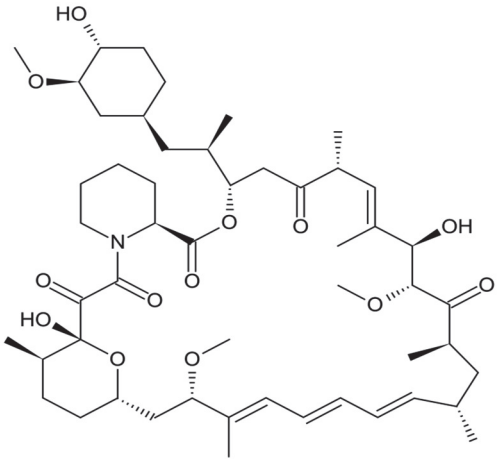

Figure 4: Chemical Structure of Sirolimus

The Svelte DES product matrix and nominal total loaded dose of sirolimus per nominal stent length/diameter is shown in **Table 2**.

Table 2. Svelte DES Product Matrix and Drug Content

Stent Design	Stent Diameters (mm)	Stent Length (mm)	Sirolimus Dose (µg/stent)	
			SLENDER IDS	DIRECT RX
3-cell	2.25 2.50 2.75 3.00	8	58	58
		13	87	87
		18	126	126
		23	156	156
		28	195	195
		33		224
		38		263
4-cell	3.50 4.00	8	79	79
		13	119	119
		18	173	173
		23	213	213
		28	266	266
		33		306
		38		360

2. Inactive Ingredient: polyesteramide (PEA)

The bioresorbable PEA carrier is a synthetic amorphous elastomeric random copolymer consisting of amino acid units (L-leucine and L-lysine benzyl ester) separated by hydrocarbon diacid (decanedioic acid) and diol (1,6-hexanediol and 1,4-dianhydrosorbitol) spacers. The structural formula of the PEA carrier is shown in **Figure 5**.

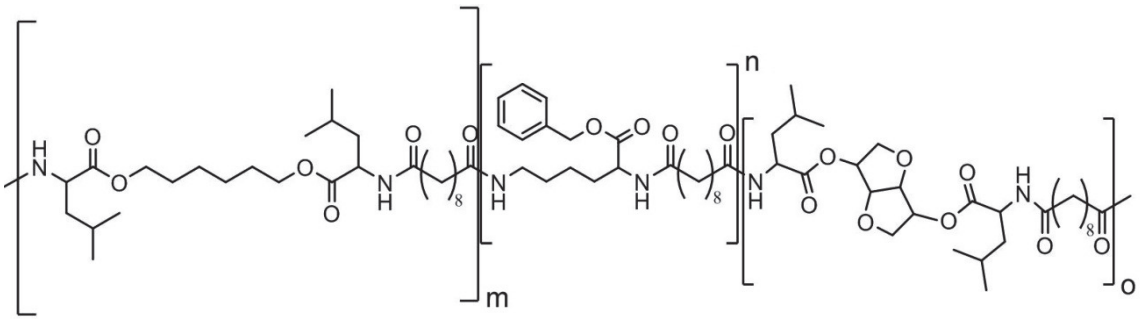

Figure 5: Chemical Structure of PEA Carrier

3. Mechanism of Action of Sirolimus

Sirolimus inhibits T-lymphocyte activation, smooth muscle and endothelial cell proliferation in response to cytokine and growth factor stimulation. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12). The sirolimus-FKBP-12 complex binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), leading to inhibition of cell cycle progression from the G_1 to S phase.

The sirolimus drug coated on the Svelte DES has an ancillary function as an anti-proliferative and anti-restenotic agent due to its ability to interrupt smooth muscle cell migration and proliferation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of coronary artery disease. These may include exercise, diet, smoking cessation, drug therapy, percutaneous coronary interventions (such as angioplasty and placement of other coronary stents), and coronary artery bypass graft surgery (CABG). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Svelte DES have been market released (CE Mark certified) outside the United States since 2016 and have been in commercial use in the Netherlands, Belgium, Czech Republic and United Kingdom. No Svelte devices have been withdrawn from distribution in any country for any reason related to product safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse events (in alphabetical order) that may be associated with the use of a stent in native coronary arteries include but are not limited to:

- Access site complications (incl. arteriovenous fistula, hematoma, infection, nerve injury, pain, peripheral ischemia, phlebitis, pseudoaneurysm)

- Acute myocardial infarction
- Acute pulmonary edema
- Allergic reaction or hypersensitivity to contrast media, antiplatelets, anticoagulants, L-605 cobalt chromium alloy, PEA, sirolimus or sirolimus derivatives
- Aneurysm formation
- Angina pectoris (stable or unstable)
- Atrial fibrillation
- Bradycardia
- Bleeding complications that may require transfusions or surgical repair
- Cardiac arrhythmias, including ventricular fibrillation and ventricular tachycardia
- Cardiac perforation
- Cardiac tamponade
- Cardiogenic shock
- Congestive heart failure
- Coronary artery complications (incl. abrupt closure, dissection, embolism, injury, perforation, plaque rupture/shift, restenosis, rupture, spasm, thrombosis, total occlusion)
- Death
- Delayed endothelialization
- Distal emboli
- Endocarditis
- Emergency cardiac surgery
- Fever or pyrogenic reactions
- Hypotension/hypertension
- Infections
- Myocardial ischemia
- Nausea and vomiting
- Palpitations
- Perforation of the heart or great vessels
- Pericardial effusion
- Respiratory insufficiency or failure
- Renal failure
- Retroperitoneal hematoma
- Stent collapse
- Stent dislodgement from the delivery system
- Stent embolization
- Stent thrombosis or occlusion
- Stroke/cerebrovascular accident/transient ischemic attack
- Vasovagal reaction
- Vasospasm
- Volume overload

Potential adverse events related to the oral administration of sirolimus include, but are not limited to:

- Abnormal liver function tests
- Anemia
- Arthralgia
- Diarrhea
- Hypercholesterolemia
- Hypersensitivity (including anaphylactic/anaphylactoid type reactions)
- Hypertriglyceridemia
- Hypokalemia
- Infections
- Interstitial lung disease
- Leukopenia
- Lymphoma and other malignancies
- Thrombocytopenia

There may be other potential adverse events that are unforeseen at this time.
For the specific adverse events that occurred in clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A series of non-clinical laboratory studies and pharmacokinetic studies related to the product were performed. Studies included those performed on the bare metal stent alone, the coated stent alone, the polymer-only coated stent alone, the delivery systems, and the finished combination product.

A. Laboratory Studies

1. In Vitro Engineering Testing

In vitro engineering testing was conducted on test samples representative of the Svelte DES in accordance with the following FDA guidance documents:

- FDA Guidance Document issued on April 18, 2010, *Non-Clinical Engineering Tests and Recommended Labelling for Intravascular Stents and Associated Delivery Systems*
- FDA Guidance Document issued on August 18, 2015, *Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*
- FDA Guidance Document issued on May 20, 2021, *Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment*

Specific in vitro engineering tests were performed on the representative uncoated, bare metal version of the Svelte DES and the delivery systems.

Table 3 summarizes this testing. "Pass" denotes that the test results met product specifications and/or the recommendations in the above referenced guidance documents.

Table 3. Summary of Engineering Testing

Test	Purpose	Acceptance Criteria	Results
Material Characterization			
Material Composition	To identify and list all components and their respective materials used in the construction of the stent and delivery systems.	The stent is fabricated from L605 CoCr alloy tubing, to which ASTM F90 applies. The incoming raw materials conform to specifications.	Pass
Stent Mechanical Properties	To test the mechanical properties for the stent tubing.	The stent tubing tensile, yield strength, and elongation must meet specification.	Pass
Stent Corrosion Resistance	To determine the stent resistance to fretting, pitting, and crevice corrosion.	Per ASTM F2129	Pass
Stent Dimensional and Functional Attributes			
Dimensional Verification (Unexpanded Stent Dimensions)	To inspect and measure the stent dimensions.	Stent dimensions must meet specifications.	Pass
Dimensional Verification (Uniformity of Stent Expansion)	To measure the diameter of the expanded stent per ASTM F2081.	The uniformity of stent expansion must meet specifications.	Pass
Percent Surface Area	To determine the surface coverage of the stent in the vessel.	Percent contact surface area must be 6-15%. The percent surface area of the stent must meet specifications.	Pass

<table>
<tr><th>Test</th><th>Purpose</th><th>Acceptance Criteria</th><th>Results</th></tr>
<tr><td>Foreshortening</td><td>To ensure the foreshortening of the stent falls within acceptable limits.</td><td>
<table>
<tr><th rowspan="2">Dia.</th><th rowspan="2">Length</th><th colspan="2">Maximum Foreshortening %</th></tr>
<tr><th>IDS</th><th>RX</th></tr>
<tr><td rowspan="2">2.25 – 2.75 mm</td><td>8 – 13 mm</td><td>≤20%</td><td>≤20%</td></tr>
<tr><td>18 – 28 mm</td><td>≤12%</td><td>≤12%</td></tr>
<tr><td rowspan="2">3.00 mm</td><td>8* – 13 mm</td><td>≤20%*</td><td>≤20%*</td></tr>
<tr><td>18 – 28 mm</td><td>≤12%</td><td>≤12%</td></tr>
<tr><td rowspan="2">3.50 mm</td><td>8 – 13 mm</td><td>≤20%</td><td>≤20%</td></tr>
<tr><td>18 – 28 mm</td><td>≤12%</td><td>≤12%</td></tr>
<tr><td rowspan="2">4.00 mm</td><td>8* – 13 mm</td><td>≤20%*</td><td>≤20%*</td></tr>
<tr><td>18 – 28 mm</td><td>≤15%</td><td>≤15%</td></tr>
</table>
*Stent sizes 3.00x8 and 4.00x8mm did not meet the acceptance criteria, with reported maximum foreshortenings of up to 21.2% and 27.4%, respectively. This was deemed acceptable based on robust scientific and clinical rationales. Accurate foreshortening percentages are in the product labeling.
</td><td>Pass</td></tr>
<tr><td>Recoil</td><td>To measure the elastic recoil of stent from its expanded diameter while still on the delivery balloon to its relaxed diameter after deflating the balloon per ASTM F2079.</td><td>Stent recoil ≤8% at nominal pressure and rated burst pressure</td><td>Pass</td></tr>
<tr><td>Stent Integrity</td><td>To examine the deployed stent for defects.</td><td>Stent will have no significant surface defects such as cracks or scratches when examined under microscope.</td><td>Pass</td></tr>
<tr><td>Radial Stiffness and Radial Strength</td><td>To characterize the ability of the stent to resist collapse under external loads.</td><td>Radial Stiffness: Characterization only

Radial Strength: Diameter decreases to 15% of starting diameter at ≥5 psi</td><td>Pass</td></tr>
</table>

Test	Purpose	Acceptance Criteria	Results
Stress/Strain and Fatigue Analysis	To identify the critical locations of stress or strain on the stent using FEA.	Goodman and Maximum Equivalent Strain Damage (MESD) analysis must demonstrate acceptable safety factors (>1).	Pass
Accelerated Durability	To determine the long-term integrity of the stent under cyclical loading conditions in an overlapping and bent configuration.	Per ASTM F2477. No stent fractures that would adversely affect stent performance after 400 million cycles (10 year equivalent)	Pass
Magnetic Resonance Imaging (MRI) Safety and Compatibility	To determine the effect of MR on the position and temperature of the stent, and to determine the extent of image artifact during MRI.	See product labeling for safe MRI use conditions	Pass
Radiopacity	To determine stent visibility using angiographic imaging to assure proper stent placement.	Stent is visible under fluoroscopy.	Pass
Delivery System Dimensional and Functional Attributes			
Dimensional Verification	To inspect and measure the dimensional properties of the stent delivery systems.	The stent delivery systems must meet dimensional specifications (e.g., length, inner and outer diameter, and crossing profile).	Pass
Delivery, Deployment, and Retraction	To evaluate the performance of the stent delivery systems to safely and reliably deliver the stent to the intended location.	The stent delivery systems can safely and reliably deliver the stent to the intended location according to the instructions for use, without damage to the stent.	Pass

Test	Purpose	Acceptance Criteria	Results
Balloon Rated Burst Pressure	To determine the rated burst pressure (RBP) of the balloon with the mounted stent.	RBP ≥18 atm The RBP label claim is the pressure at which 99.9% of the balloons can survive with 95% confidence.	Pass
Balloon Fatigue	To determine the ability of the balloon to withstand repeated inflation/ deflation cycles.	The balloon catheter must demonstrate that 90% of the balloons will survive 10 inflations to RBP, with 95% confidence and maintain pressure per specification.	Pass
Balloon Compliance (Stent Diameter vs. Balloon Pressure)	To determine the relationship between the stent diameter and the balloon inflation pressure.	To generate a compliance chart in the labeling that relates stent diameter to balloon pressure.	Pass
Balloon Inflation and Deflation Time	To determine the amount of time required to inflate or deflate the balloon delivery systems.	Inflation Time: Characterization of time to inflate the balloon to targeted label RBP. Deflation Time: IDS: Upper STI of Deflation Time ≤20 seconds from RBP RX: Upper STI of Deflation Time ≤30 seconds from RBP	Pass
Catheter Bond Strength and Tip Pull Test	To determine the bond strengths of the delivery systems and their tips	Catheter bond strengths must meet specifications.	Pass
Flexibility and Kink Test	To demonstrate the smallest radius that the delivery systems can conform to prior to kinking.	The stent delivery systems will not kink or exhibit a diameter reduction affecting the performance while traversing vessels with a bend radius of 0.50 in (12.7 mm).	Pass
Catheter Torque Strength	To demonstrate that the delivery systems can withstand torsional forces that are typical of clinical use.	IDS & RX: Withstand 15 full rotations without failure. IDS Only: Hold pressure to targeted label RBP for 30 seconds after 3 full rotations.	Pass

Test	Purpose	Acceptance Criteria	Results
Coating Integrity	To demonstrate minimal degradation of the coating on the stent delivery systems during acute clinical performance.	Characterization only	Pass
Stent Securement	To measure the force that will dislodge the stent prior to deployment.	Stent dislodgement by forward motion and reverse motion: Lower STI ≥0.5N	Pass

2. Coating Characterization Testing

The coating characterization testing conducted on the Svelte DES is summarized in **Table 4**.

Table 4. Coating Characterization Testing

Test	Purpose	Acceptance Criteria	Results
Acute Particulate Evaluation – Baseline unconstrained expansion to RBP	To measure the particulate matter generated by the stent during unconstrained expansion to RBP without tracking.	Characterization only	Pass
Acute Particulate Evaluation – Simulated use	To measure the particulate matter generated during simulated use of the delivery system through an in vitro model to maximum dilatation limit in an overlapping configuration in a mock vessel with 15mm bend radius.	Characterization only	Pass
Acute Coating Integrity	To assess the drug coating integrity of the stent as manufactured (e.g. prior to tracking and expansion).	Characterization only	Pass
Acute Coating Durability	To assess the durability of the coating when subjected to simulated clinical use conditions.	Characterization only	Pass

Test	Purpose	Acceptance Criteria	Results
Chronic Coating Integrity, including Particulate Evaluation	Particulate evaluation and coating integrity assessment of stents in bent overlapped configuration after exposure to pulsatile stresses and strains.	Characterization only	Pass
Coating Thickness and Uniformity	To measure the coating thickness along the length of the expanded stent post deployment to RBP for both the abluminal and luminal stent surfaces. To analyze the coating uniformity along the length and circumference of the stent via assaying individual stent segments for sirolimus.	Characterization only	Pass
Coating Characterization – Adhesion of the coating to the stent substrate	To measure the coating adhesion (delamination strength) of the expanded stent post deployment to RBP.	Characterization only	Pass

3. Chemistry, Manufacturing & Controls (CMC) Release Testing

Each batch of finished devices undergoes testing prior to release and distribution. Where applicable, the test methods follow International Conference on Harmonization (ICH) guidelines. This testing is summarized in **Table 5**.

Table 5. CMC Release Testing

Test	Purpose
Drug Identity	To verify the identity of the drug substance in the finished stent.
Drug Content	To verify that the total amount of the drug on the stent is within the specifications established for the finished product.
Content Uniformity	To verify the uniformity of the drug content between individual stents is within the specifications established for the finished stent.
Related Substances	Testing is conducted to verify that the amount of impurities are within the specifications established for the finished product.

Test	Purpose
Drug Release	To verify that the in vitro release of the drug substance is within the specifications established for the finished product.
BHT Content	Testing is conducted to verify that the amount of BHT is within the specifications established for the finished product.
Particulate Matter	To verify that particle counts are below acceptable levels for the finished product.
Molecular Weight	Testing is conducted to verify that the molecular weight of the polymer in the drug coating is within the specifications established for the finished product.
Bacterial Endotoxins	To verify that endotoxin levels are within specifications established for the finished product.
Sterility	To verify the sterility of the finished product.

4. Stability and Shelf Life

Stability/shelf-life studies were conducted to establish a shelf life for the Svelte DES. The stability testing included a combination of real time and accelerated aging stability studies for drug properties, particulate matter, packaging integrity and sterility, polymer coating properties, and relevant engineering attributes of the stent and delivery system. The data generated supports a product shelf life of 2 years.

5. Packaging and Sterilization

Packaging verification testing was performed to demonstrate that the design of the Svelte DES packaging can withstand the hazards of the distribution environment and that the sterility of the product is maintained throughout the labeled shelf life. The Svelte DES are sterilized with ethylene oxide (EtO) gas to a sterility assurance level (SAL) of $1x10^{-6}$. The quantity of bacterial endotoxins was verified to be within the specification limits. The sterilization processes are in compliance with EN ISO 11135:2014.

6. Biocompatibility

A series of Good Laboratory Practice (GLP) biocompatibility tests and USP Physicochemical tests were conducted to demonstrate that the components of the Svelte DES are non-toxic and biocompatible. Tests were conducted on final, ethylene oxide sterilized coated stents, polymer only coated stents, uncoated stents, stent delivery systems and the insertion tool accessory device. These test articles were processed in the same manner as the finished Svelte DES. The results of the biocompatibility studies indicated that the Svelte DES was biologically safe and acceptable for clinical use:

All biocompatibility testing was conducted in accordance with one or more of the following general regulations, standards and guidance documents:

- Good Laboratory Practices Regulations (21 CFR § 58)
- ISO 10993-1:2018, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
- AAMI / ANSI / ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
- FDA Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process", Guidance for Industry and Food and Drug Administration Staff, June 16, 2016
- USP "Physicochemical Test – Containers Plastics" <661>

Table 6 provides a summary of the biocompatibility testing conducted to support the Svelte DES.

Table 6. Summary of Biocompatibility Testing

Test Name	Test Description	Test Article	Result
Chemical Characterization	ISO 10993-18: Chemical Characterization of Materials Extraction of Chemical Compounds	• Coated (drug and polymer blend) stent	Extractables/ leachables not of toxicological concern for applicable endpoints
Cytotoxicity	ISO 10993-5: *In vitro* Cytotoxicity (L929 MEM Elution)	• Coated (drug and polymer blend) stent • Polymer only coated stent • Uncoated stent • IDS Delivery System • RX Delivery System • Insertion Tool	Pass (non-cytotoxic)
	ISO 10993-5: *In vitro* Cytotoxicity (Neutral Red Uptake)	• Coated (drug and polymer blend) stent • Polymer only coated stent	
Sensitization	ISO 10993-10: Sensitization Kligman Maximization (Guinea Pig)	• Coated (drug and polymer blend) stent • Uncoated stent • IDS Delivery System • RX Delivery System	Pass (non-sensitizer)
Intracutaneous Reactivity	ISO 10993-10: Intracutaneous Injection (Rabbit)	• Coated (drug and polymer blend) stent • Uncoated stent • IDS Delivery System • RX Delivery System	Pass (non-irritant)

Test Name	Test Description	Test Article	Result
Pyrogenicity	ISO 10993-11: Material Mediated Pyrogenicity (Rabbit)	• Coated (drug and polymer blend) stent • Uncoated stent • IDS Delivery System • RX Delivery System	Pass (non-pyrogenic)
Systemic Toxicity (Acute)	ISO 10993-11: Systemic Injection (Mouse)	• Coated (drug and polymer blend) stent • Uncoated stent • IDS Delivery System • RX Delivery System	Pass (non-toxic)
Systemic Toxicity (Subchronic)	ISO 10993-6 and ISO 10993-11: 90 Day Subcutaneous Implantation (Rabbit)	• Coated (drug and polymer blend) stent	Pass (non-toxic)
	ISO 10993-6 and ISO 10993-11: 90 Day Intramuscular Implantation (Rat)	• Uncoated stent	
Systemic Toxicity (Chronic)	ISO 10993-6 and ISO 10993-11: 26 Week Subcutaneous Implantation (Rat)	• Coated (drug and polymer blend) stent	Pass (non-toxic)
Implantation	ISO 10993-6: 7 Day Intramuscular (Rabbit)	• Coated (drug and polymer blend) stent	Pass (non-toxic, non-irritant)
	ISO 10993-6: 4 Week Intramuscular (Rabbit)		
Hemocompatibility	ISO 10993-4: Thrombogenicity (Dog)	• Coated (drug and polymer blend) stent • Uncoated stent • IDS Delivery System	Pass (non-thrombogenic)
	ISO 10993-4: Thrombogenicity (Swine)	• RX Delivery System	
	ASTM F756: *In vitro* Hemolysis (Rabbit Blood - Direct & Indirect Contact)	• Coated (drug and polymer blend) stent • Uncoated stent • IDS Delivery System • RX Delivery System	Pass (non-hemolytic)
	ISO 10993-4: *In vitro* Hemocompatibility (Human Blood - Direct Contact)	• Coated (drug and polymer blend) stent • Uncoated stent	Pass (no effect on hematology)
	ISO 10993-4: *In vitro* Hemocompatibility (Human Blood - Indirect Contact)	• Coated (drug and polymer blend) stent	
	ISO 10993-4: *In vitro* UPTT (Human Plasma - Direct Contact)	• Coated (drug and polymer blend) stent • Uncoated stent	Pass (no effect on clotting time)
	ISO 10993-4: *In vitro* Complement Activation-C3a and SC5b-9 (Human Plasma - Direct Contact)	• Coated (drug and polymer blend) stent • Uncoated stent • IDS Delivery System • RX Delivery System	Pass (no activation of complement)

Test Name	Test Description	Test Article	Result
Genotoxicity	ISO 10993-3: *Salmonella Typhimurium* and *Escherichia Coli* Reverse Mutation Assay (Ames)	• Polymer only coated stent • Uncoated stent • IDS Delivery System • RX Delivery System	Pass (non-mutagenic)
	ISO 10993-3: Mouse Lymphoma Forward Mutagenesis Assay	• Polymer only coated stent • Uncoated stent	Pass (non-mutagenic)
	ISO 10993-3: Mouse Peripheral Blood Micronucleus Study	• Polymer only coated stent	Pass (non-mutagenic)
	ISO 10993-3: Rodent Bone Marrow Micronucleus Study	• Uncoated stent	Pass (non-mutagenic)
Carcinogenicity	Chemical Characterization: Extractable/Leachable Chemical Compounds and Toxicological Risk Assessment	• Coated (drug and polymer blend) stent	Pass based on toxicological risk assessment
Reproductive Toxicity			
Degradation	Chemical Characterization: *In vitro* Polymer Intermediate Degradation Products and Toxicological Risk Assessment	• Coated (drug and polymer blend) stent	Pass based on toxicological risk assessment
Physiochemical	USP 39/ NF 34 Supplement 2, <661.2> - Absorbance	• Insertion Tool	Pass
	USP 39/ NF 34 Supplement 2, <661.2> - Alkalinity or Acidity		Pass
	USP 39/ NF 34 Supplement 2, <661.2> - Total Organic Carbon		Pass

Genotoxicity, carcinogenicity and reproductive toxicity testing on the finished drug and polymer coated Svelte DES were not conducted based on a chemical characterization and toxicological assessment along with the negative results of genotoxicity testing of the uncoated and polymer only coated stents, which showed no toxicological concern for these endpoints.

A toxicological risk assessment was conducted on the degradants from the PEA in the stent coating and was found to be acceptable.

Based on the known molecular structures and properties and *in vitro* analytical and stability testing results, there is no evidence to suggest that any chemical interactions occur between the PEA carrier and the sirolimus drug under the established processing and storage conditions that would lead to the formation of covalent bonds or that would alter the structure of the drug in any way to form a new intermediate or molecular entity.

B. Animal Studies

A series of animal studies were conducted to evaluate safety, efficacy, and overall product performance.

To assess the safety, acute performance and certain biocompatibility endpoints of the Svelte DES, SLENDER IDS and DIRECT RX delivery systems, animal studies were conducted to evaluate the inflammation, neointimal proliferation, endothelialization, necrosis, thrombogenicity, embolism, pharmacokinetics, polymer degradation kinetics, device deliverability and radiopacity. The animal studies also included high dose and overlapping DES evaluations. Quantitative angiography, gross evaluation, quantitative histomorphometry and histopathology were performed for stents implanted in the coronary arteries as well as downstream myocardial assessments. All Svelte stents that were successfully implanted remained structurally intact for the duration of implantation.

All animal studies were performed using healthy pigs in accordance with the Good Laboratory Practice (GLP) for Non-clinical Laboratory Studies requirements outlined in 21 CFR Part 58, unless otherwise noted below. The results of these studies support the safety and biocompatibility of the Svelte DES. A summary of the major animal studies performed to support product safety are shown in **Table 7** below.

Table 7. Summary of Major Supportive Animal Studies

Study Type	Test Article Size Treatment PEA/API ratio Dosage/stent Dose Density	Type: Number of Animals	Number of Stents	Evaluation Time Points	Testing Objectives Major Endpoints
Chronic Tissue Response Safety Study (GLP)	Svelte DES-IDS 3.00x18mm single & overlapped 70/30 API: 126µg 213 µg/cm^2	Yucatan miniswine: 69	Test: 88 Controls BMS: 34 XIENCE DES: 60	3, 30, 90, 180 and 390 days	Acute performance (preparation, delivery, deployment, thrombogenicity) Angiographic analysis Clinical Pathology Radiography Histopathology Morphometric analysis SEM analysis Myocardial assessment
High Dose Tissue Response Safety Study (GLP)	Svelte HD-DES 3.00x18mm 100% overlapped 70/30 API: 278µg 469 µg/cm^2 2.2x coating	Yucatan miniswine: 12	Test: 48 Control BMS: 24	30 and 90 days	Angiographic analysis Clinical Pathology Radiography Histopathology Morphometric analysis Myocardial assessment
Pharmacokinetic, Carrier Degradation Kinetics Study	Svelte DES-IDS 3.00x18mm single 70/30 API: 124µg 213 µg/cm^2	Yucatan miniswine: 15	Test: 45	30, 60, 90, 120, 180, 270, 360 days	Angiographic analysis Stent PEA carrier content at explant
				0, 1, 5, 15, 30, 60 mins 2, 4, 6, 8, 24 hrs 2, 3, 4, 8, 12, 14 days	Drug concentration - blood

Study Type	Test Article Size Treatment PEA/API ratio Dosage/stent Dose Density	Type: Number of Animals	Number of Stents	Evaluation Time Points	Testing Objectives Major Endpoints
Pharmacokinetic Study	Svelte DES-IDS 3.00x18mm single 70/30 API: 124µg 213 µg/cm^2	Yorkshire swine: 6	Test: 36	1, 3, 8, 14, 30 and 60 days	Angiographic analysis Stent drug content at explant Drug concentration - arterial tissue at explant
Chronic Carrier Only Tissue Response Safety Feasibility Study	Svelte DES-IDS 3.00x18mm 70/30 single API: 124µg 213 µg/cm^2	Yucatan miniswine: 27	Test: 24 Controls PEAS: 20 BMS: 26 XIENCE: 8	30, 90 and 390 days	Acute performance (preparation, delivery, deployment, thrombogenicity) Angiographic analysis Clinical Pathology Radiography Histopathology Morphometric analysis SEM analysis Myocardial assessment
RX Acute Performance and Thrombogenicity Assessment Study (GLP)	Svelte DES-RX 2.50x18mm 3.00x18mm single 70/30 API: 126µg 213 µg/cm^2	Yorkshire swine: 3	Test: 10	0 and 3 days	Acute performance (preparation, delivery, deployment, thrombogenicity) Angiographic analysis Clinical Pathology Histopathology Histomorphology Myocardial assessment Non-cardiac organ assessment
IDS Acute Performance Assessment Study (non-GLP)	Svelte BMS-IDS 2.50x13mm Single	Yucatan swine: 1	Test: 4	0 days	Acute performance (preparation, delivery)
IDS Acute Performance Assessment Study (GLP)	Svelte BMS-IDS 4.00x28mm Single	Yorkshire swine: 3	Test: BMS: 5 IDS: 8 Control Vision Stent: 5 SDS: 8	0 days	Acute performance (preparation, delivery, deployment, thrombogenicity) Angiographic analysis Heart necropsy

C. Additional Studies

1. In Vivo Pharmacokinetics

A prospective, open, non-randomized human pharmacokinetic (PK) study was conducted in the United States. A total of eight patients with symptomatic ischemic

heart disease were consented and treated from December 2018 through April 2019. At least 38% (3 patients) received a sufficiently large stent so that the total implanted stent dose was >1.7 times the sirolimus dose of the workhorse Svelte DES (3.0x18mm). Blood samples were drawn to evaluate the systemic PK parameters of sirolimus release from the implanted Svelte DES.

For each patient, peripheral blood samples were collected at 10 and 30 minutes, at 1, 2, 4, 6, 12, 24, 48, and 72 hours, and at 7, 14, and 30 days post-stent implantation with continued follow-up for 2 years. Whole blood concentration of sirolimus was determined using a validated high performance liquid chromatography mass spectrometry (HPLC-MS) method. PK parameters were calculated and summarized in **Table 8**. Terms and definitions of PK parameters are shown in **Table 9**.

Table 8. Individual and Mean PK Parameters for Sirolimus

Subject	λ_z	Thalf	Tmax	Cmax	AUClast	AUCINF	Vz/F	CL/F	CL/F Normalized	Vz/F Normalized
	1/hr	hr	hr	ng/mL	hr*ng/mL	hr*ng/mL	L	L/hr	L/hr/kg	L/kg
1	0.00277	251	4.32	0.436	68.0	105	434	1.20	12.8	4.62
2	0.00182	382	1.93	0.754	179	243	596	1.08	12.0	6.64
3	0.00165	419	2.15	0.713	174	249	378	0.63	6.96	4.21
4	0.00364	191	1.98	0.457	69.9	94.9	502	1.82	15.9	4.37
5	0.00206	336	3.95	1.56	409	528	330	0.68	7.59	3.68
6	0.00331	209	0.450	0.539	75.5	116	553	1.83	11.7	3.52
7	0.00266	260	1.15	0.500	138	161	278	0.74	8.33	3.13
8	0.00199	348	1.02	0.564	165	219	357	0.71	7.76	3.90
N	8	8	8	8	8	8	8	8	8	8
Mean	0.00249	299	2.12	0.690	160	215	429	1.09	10.4	4.26
STD	0.00073	83.5	1.37	0.369	111	141	113	0.500	3.19	1.08
Min	0.00165	191	0.450	0.436	68.0	94.9	278	0.625	6.96	3.13
Median	0.00236	298	1.96	0.552	151	190	406	0.911	10.0	4.06
Max	0.00364	419	4.32	1.56	409	528	596	1.83	15.9	6.64
CV%	29.2	27.9	64.8	53.5	69.7	65.7	26.3	46.0	30.7	25.2
Geometric Mean	N/A	N/A	N/A	0.632	134	184	N/A	N/A	N/A	N/A
Geometric CV	N/A	N/A	N/A	43.2	67.9	62.3	N/A	N/A	N/A	N/A

N/A = Not Applicable

Table 9. Terms and Definitions of PK Parameters

Term	Definition
AUC_{inf}	Area under the curve to infinite time ($AUC_{0\text{-}inf}$)
AUC_{last}	Area under the curve to the last measured concentration ($AUC_{0\text{-}t}$)
CL/F	Clearance of drug
C_{max}	Peak drug concentration
T_{half}	Drug elimination half-life
T_{max}	Time to peak drug concentration
Vz/F	Volume of drug distribution
Λz	Apparent terminal first-order elimination rate constant

Results obtained from the PK study:

- Stent nominal sirolimus dose ranged from 119 to 360 μg/stent (DES implants from 3.50x13mm to 4.00x38mm).
- Whole blood C_{max} values increased with increasing dose and ranged from 0.436 to 1.56 ng/mL.
- AUC_{last} and AUC_{inf} values ranged from 68.0 to 409 hr*ng/mL and 94.9 to 528 hr*ng/mL, respectively.
- The drug elimination half-life of sirolimus ranged from 191 to 419 hrs across all dose levels.
- The systemic clearance of sirolimus ranged from 6.96 to 15.9 L/hr/kg across all dose levels.
- A dose-proportional linear trend was observed for C_{max}, AUC_{last}, and AUC_{inf} over a 3-fold range of both total stent sirolimus dose and normalized patient dose.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study, OPTIMIZE, to establish a reasonable assurance of safety and effectiveness of the Svelte DES for improving coronary artery luminal diameter in patients with symptomatic heart disease due to atherosclerotic lesions ≤24 mm in length in native coronary arteries with ≥2.25 mm to ≤4.00 mm reference vessel diameters, using direct stenting or pre-dilatation interventional techniques in the United States, Japan and the Netherlands under IDE # G160227. Data from this clinical study were the basis for the PMA approval decision. Data from the previous DIRECT I-III studies conducted outside of the US were provided as supplemental, non-primary clinical data; these studies are described in **Section XI**. A summary of the pivotal OPTIMIZE study is presented below.

A. Study Design

Patients were treated between January 2, 2018 and June 4, 2019. The database for this PMA reflected data collected through June 25, 2020 and included 1639 patients. There were 74 investigational sites.

The study was a prospective, single-blind, randomized (1:1), active-control, multi-center clinical study to compare the safety and effectiveness of the Svelte DES to coronary drug-eluting stents (DES) (Abbott Vascular XIENCE or Boston Scientific Promus). The control treatments were legally marketed alternatives with similar indications for use.

Patients were randomized 1:1 to the Svelte DES (SLENDER IDS or DIRECT RX at investigator discretion), or the XIENCE DES or Promus DES (control DES pooled group).

For each treatment group, the number and percentage of patients with 12-month TLF were summarized. The risk difference and the two-sided 95% confidence interval of the risk difference between two treatment groups were calculated based on the Farrington-Manning test. The null hypothesis was also tested using the Farrington-Manning test, as

was an assessment of the poolability of the Control DES (XIENCE or Promus DES) to confirm consistency of results.

OPTIMIZE utilized an independent angiographic core laboratory and independent clinical events committee (CEC) to evaluate and adjudicate study primary and secondary endpoint data. The core laboratories and CEC were composed of experts in their field.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the OPTIMIZE study was limited to patients who met the following inclusion criteria:

General Inclusion Criteria:

1. Subject is ≥ 18 years old;
2. Subject understands the study requirements, the treatment procedures and provides written informed consent before any study-specific tests or procedures are performed;
3. Subject is an eligible candidate for PCI;
4. Subject has symptomatic coronary artery disease with objective evidence of ischemia or silent ischemia;
5. Subject has clinical symptoms or ECG changes consistent with non-ST elevation MI (NSTEMI), is clinically and hemodynamically stable and has cardiac enzymes documented to be decreasing prior to the study procedure (CK-MB is preferred, but if troponin is assessed, enzymes decreasing, stable or elevated up to 20% over the prior assessment are acceptable);
6. Subject is an acceptable candidate for CABG;
7. Subject agrees to comply with specified follow-up evaluations.

Angiographic Inclusion Criteria (visual estimate):

1. Subject has ≤3 de novo target lesions in ≤2 native coronary artery vessels, with ≤2 lesions in a single vessel, each meeting the angiographic criteria and none of the exclusion criteria.
2. Target lesion(s) must be located in a native coronary artery with RVD ≥2.25 mm and ≤4.00 mm;
3. Target lesion(s) length must be ≤34 mm in length (the intention should be to cover the whole lesion with one stent of adequate length);
4. Target lesion(s) must have visually estimated stenosis ≥50% and <100% with Thrombolysis in Myocardial Infarction (TIMI) flow >1. For lesions with visually estimated stenosis ≥50% and ≤70%, additional confirmation by ACC/AHA guideline compliant physiologic assessment is required;
5. Coronary anatomy is likely to allow delivery of a study device(s) to the target lesion(s).

Patients were not permitted to enroll in the OPTIMIZE study if they met any of the following exclusion criteria:

General Exclusion Criteria:

1. Subject has clinical symptoms or electrocardiogram (ECG) changes consistent with acute ST elevation MI (STEMI). Subject may be included if primary PCI for STEMI was successfully completed and subject is clinically and hemodynamically stable with cardiac enzymes documented to be decreasing ≥72 hours prior to the study procedure;
2. Subject has cardiogenic shock, hemodynamic instability requiring inotropic or mechanical circulatory support, intractable ventricular arrhythmia, or ongoing intractable angina;
3. Subject has received an organ transplant or is on a waiting list for an organ transplant;
4. Subject is receiving or scheduled to receive chemotherapy 30 days before or after the index procedure;
5. Subject requires a planned PCI (including staged procedures), CABG or surgical or catheter-based valvular intervention within 12 months of the index procedure;
6. Subject was previously treated at any time with intravascular brachytherapy;
7. Subject has a known allergy to contrast (that cannot be adequately premedicated) and/or the study stent systems or protocol-required concomitant medications (e.g., platinum, platinum-chromium alloy, stainless steel, sirolimus, everolimus or structurally related compounds, polymer or individual components, all P2Y12 inhibitors or aspirin);
8. Subject has one of the following (as assessed prior to the index procedure):
    a. Other serious medical illness (e.g., cancer, congestive heart failure) with estimated life expectancy of <24 months;
    b. Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.);
    c. Planned procedure that may cause non-compliance with the protocol or confound data interpretation;
9. Subject is receiving chronic (≥72 hours) anticoagulation therapy (e.g., heparin, coumadin) for indications other than acute coronary syndrome (ACS);
10. Subject has a platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3;
11. Subject has a white blood cell (WBC) count <3,000 cells/mm^3;
12. Subject has documented significant liver disease, including laboratory evidence of hepatitis;
13. Subject is on dialysis or has a baseline serum creatinine level >2.0 mg/dL (177 μmol/L);
14. Subject has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions;
15. Subject has a history of cerebrovascular accident (CVA) or transient ischemic attack (TIA) within the past 6 months;
16. Subject has an active peptic ulcer or active gastrointestinal (GI) bleeding;
17. Subject has severe symptomatic heart failure (i.e., NYHA class IV);
18. Subject intends to participate in another investigational drug or device clinical study within 12 months after the index procedure;
19. Subject has a known intention to procreate within 12 months after the index procedure (a woman of child-bearing potential who is sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure);

20. Subject is pregnant or nursing (subject must have a negative pregnancy test within 14 days prior to the index procedure if a woman of child-bearing potential);
21. Subject is participating in another investigational drug or device clinical study;
22. Planned use of cutting balloon or atherectomy (rotational, orbital, laser or other) or any other form of treatment of the target lesion(s) during the index procedure other than plain balloon angioplasty and the randomized stent.

Angiographic Exclusion Criteria (visual estimate):

1. Subject has a planned treatment of >3 lesions;
2. Subject has a planned treatment of >2 major epicardial vessels;
3. Subject has a planned treatment of a single lesion with >1 stent;
4. Subject has 2 target lesions in the same vessel that are separated by <15 mm;
5. Subject's target lesion(s) is located in the left main coronary artery;
6. Subject's target lesion(s) is located within 3 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCX) coronary artery;
7. Subject's target lesion(s) is located within a saphenous vein graft (SVG) or an arterial graft;
8. The subject's target lesion(s) will be accessed via SVG or arterial graft;
9. Subject has a target lesion(s) with TIMI flow 0 (total occlusion) or TIMI flow 1 prior to guide wire crossing;
10. Subject's target lesion(s) involves a complex bifurcation (e.g., bifurcation lesion requiring treatment with more than one stent);
11. Subject's target lesion is located within 10 mm of a previously implanted stent or involves in-stent restenosis;
12. Subject has unprotected left main coronary artery disease (>50% diameter stenosis);
13. Subject has been treated with any type of PCI (i.e., balloon angioplasty, stent, cutting balloon, or atherectomy) within 24 hours of the index procedure
14. Subject has thrombus or possible thrombus present in the target vessel.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 12 months post-procedure. Telephone assessments were scheduled for 1 month, 6 months, 2 years, and annually through 5 years. Due to the COVID-19 global pandemic, some 12-month assessments were conducted via telephone. The first 150 patients enrolled were assigned to receive angiographic evaluation at the index procedure and at 12-month follow up. The first 60 patients were also assigned to have IVUS performed at the index procedure and 12-month follow up.

Preoperatively, patients received physical examinations, angina status was recorded, routine laboratory tests including cardiac enzyme assessments were conducted, and 12-lead electrocardiograms were performed. Postoperatively, prior to discharge, patients received another physical examination, angina status was recorded, cardiac enzymes were drawn (4 – 2 hours post-procedure and again 12 – 20 hours post-procedure or at discharge), another ECG was performed, and all adverse events were recorded. At follow-up visits and calls, angina assessment, cardiovascular and other important medication intake, and any adverse events were recorded.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

The primary endpoint was a composite of outcomes related to both safety and effectiveness: target lesion failure (TLF) at 12 months, defined as cardiac death, target vessel myocardial infarction (TVMI) (Q-wave or non-Q-wave; MI defined below), or clinically-indicated target lesion revascularization (TLR).

With regards to safety, secondary clinical outcomes evaluated at all study timepoints included the following:

- Death (all cause)
- Cardiac death
- TVMI
- Stent thrombosis according to Academic Research Consortium (ARC) criteria

With regards to effectiveness, the primary endpoint of the angiographic substudy was 12-month in-stent late lumen loss (LLL). Post-procedural secondary endpoints included the following:

- Device Success: Attainment of <30% final residual stenosis of the target lesion using only the randomized stent;
- Lesion Success: Attainment of <30% final residual stenosis of the target lesion using any stent, with or without other interventional devices;
- Procedure Success: Lesion success and no in-hospital major adverse cardiac events (MACE);
- Direct Stent Strategy Success: Attainment of <30% final residual stenosis of the target lesion without pre-dilatation if the operator had originally chosen to proceed using a direct stent approach.

Clinical effectiveness endpoints included clinically-driven TLR and clinically-driven target vessel revascularization (TVR) at all study timepoints.

With regards to success/failure criteria, non-inferiority testing of the primary endpoint was planned. Assuming a 12-month TLF rate of 6.5% and an absolute non-inferiority margin of 3.58% with a one-sided alpha of 0.025, a total of 1,548 patients had 80% power to demonstrate non-inferiority of TLF at 12 months follow up. To account for loss to follow-up (expected to be approximately 5%), a total of 1,630 patients were required to be randomized. The assumption of the 12-month TLF rate of 6.5% was based on the rate of 12-month TLF observed for Promus in the EVOLVE II study, which used the same patient selection criteria.

The non-inferiority null and alternative hypotheses were:

- H_0: $\pi_{SV} - \pi_C \geq 0.0358$
- H_1: $\pi_{SV} - \pi_C < 0.0358$

where π_{SV} and π_C are the true 12-month TLF rate for Svelte DES and the combined control group of XIENCE or Promus DES, respectively, and 0.0358 is the non-inferiority margin. The one-sided significance level was 0.025. For each treatment group (Svelte DES vs. combined control DES), the number and percentage of patients with 12-month TLF were presented, as was the risk difference and the two-sided 95% confidence interval of the risk difference, calculated using the Farrington-Manning test. The primary endpoint was evaluated on an intent-to-treat (ITT) basis.

The angiographic substudy's non-inferiority null and alternative hypotheses were:

- H_0: $\mu_{SV} - \mu_C \geq 0.20$
- H_1: $\mu_{SV} - \mu_C < 0.20$

where μ_{SV} and μ_C were the true mean 12-month in-stent LLL for Svelte DES and the control DES, respectively, and 0.20 was the non-inferiority margin. The one-sided significance level was 0.05. For each treatment group (Svelte DES vs. control DES), descriptive statistics (sample size, mean, median, standard deviation, minimum and maximum) of in-stent 12-month in-stent LLL were presented, as was the difference between means and the one-sided 95% confidence interval of the difference between means. The null hypothesis was tested using a two-sample t-test.

Protocol Definition of MI: All MI was assumed target vessel (a component of the primary endpoint) unless objective evidence presented otherwise. The protocol definition of MI was identical to that used in the EVOLVE II study, which was itself a modification of the first Academic Research Consortium (ARC) definition (2006) and the 2007 Global Task Force Universal definition of peri-procedural MI [1] [2] [3]. The OPTIMIZE MI definition was as follows:

Spontaneous MI: Detection of rise and/or fall of cardiac biomarkers (CK-MB or troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

1. Symptoms of ischemia;
2. ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
3. Development of pathological Q waves in the ECG;
4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Percutaneous Coronary Intervention-Related MI: Peri-procedural PCI MI was defined by any of the following criteria. Symptoms of cardiac ischemia were not required.

1. Biomarker elevations within 48 hours of PCI:
   - CK-MB > 3X URL or
   - CK-MB not measured and CK > 2X URL or
   - Neither CK-MB nor CK measured and troponin > 3X URL

   AND

No evidence that cardiac biomarkers were elevated prior to the procedure OR both of the following must have been true:

- ≥50% increase in cardiac biomarker result
- Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-hours apart) prior to the suspected MI

2. New pathological Q waves
3. Autopsy evidence of acute MI

B. Accountability of PMA Cohort

At the time of database lock, of 1639 patients enrolled in the PMA study, 95.3% (1563) are available for analysis at the completion of the study, the 12-month post-index procedure visit. The disposition of the patients is summarized in **Table 10**.

Table 10. Patient Disposition

Patient Disposition	Svelte DES	Control DES	Total
Signed Informed Consent	N/A	N/A	6184
Screen Failures	N/A	N/A	4542
Number of Patients Randomized (ITT Population)	827	812	1639
Deaths Prior to 12-Month Visit	0.7% (6/827)	1.1% (9/812)	0.9% (15/1639)
Withdrew Consent/Lost to Follow-up/Other	1.7% (14/827)	1.8% (15/812)	1.8% (29/1639)
Missed 12-Month Visit	2.2% (18/827)	1.7% (14/812)	1.9% (32/1639)
Completed 12 Month Visit	95.4% (789/827)	95.3% (774/812)	95.4% (1563/1639)
Primary Endpoint Evaluable Patients	96.2% (796/827)	96.0% (780/812)	96.2% (1576/1639)

The intention-to-treat (ITT) population consisted of all 1639 patients randomized in the study. Patients exiting the study early for reasons marked as “other” include those where the investigative site discontinued intent-to-treat follow-up in error due to not receiving a study stent, being randomized in error and no study procedure occurring. "Primary-Endpoint Evaluable Patients" are defined as patients 1) experiencing a TLF event within 12 months of the study procedure, or 2) completing clinical follow-up ≥ 330 days after the study procedure.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are relatively typical for a coronary stent study performed in the US. **Table 11** presents demographics for the OPTIMIZE study ITT population. The mean age of the study patients was 65.4 years and 28.25% were female. Patients were predominantly white (81.9%) and overweight (mean body mass index (BMI) 29.4 kg/m^2).

Table 11. OPTIMIZE Study Baseline Demographics

Patient Characteristics	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)
Age (years)		
Mean±SD (N)	65.09±10.02 (827)	65.79±10.33 (812)
Range (min, max)	(25.00,89.00)	(36.00,90.00)
Sex		
Male	72.67% (601/827)	70.81% (575/812)
Female	27.33% (226/827)	29.19% (237/812)
Race		
American Indian or Alaska Native	0.24% (2/827)	0.25% (2/812)
Asian	10.88% (90/827)	10.96% (89/812)
Black or African American	3.87% (32/827)	3.33% (27/812)
Native Hawaiian or Pacific Islander	0.24% (2/827)	0.00% (0/812)
White	81.38% (673/827)	82.39% (669/812)
Other	0.85% (7/827)	0.62% (5/812)
Ethnicity		
Hispanic or Latino	2.78% (23/827)	2.83% (23/812)
BMI (kg/m^2)	29.08±5.69 (826)	29.20±5.92 (811)

Error! Not a valid bookmark self-reference. shows the baseline clinical characteristics and medical history of the ITT population. Groups were evenly matched, with the majority of patients reporting prior or current smoking, hypertension and hyperlipidemia. Approximately 30% of patients were diabetic, consistent with previously reported and recent prospective studies.

Table 12: Baseline Clinical Characteristics

Parameter	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)
Smoking Status		
Never Smoked	36.28% (300/827)	38.67% (314/812)
Previous Smoker	47.52% (393/827)	44.09% (358/812)
Current Smoker	16.20% (134/827)	17.24% (140/812)
History of MI	31.44% (260/827)	32.76% (266/812)
Previous Revascularization	36.88% (305/827)	34.48% (280/812)
Previous PCI	93.77% (286/305)	93.93% (263/280)
Previous CABG	11.80% (36/305)	11.07% (31/280)
History of Stroke	3.51% (29/827)	5.30% (43/812)
History of Transient Ischemic Attack	3.99% (33/827)	4.31% (35/812)
Congestive Heart Failure	6.89% (57/827)	5.91% (48/812)
Diabetes	28.54% (236/827)	30.67% (249/812)
Insulin-Dependent	30.51% (72/236)	27.31% (68/249)
Non Insulin-Dependent	69.49% (164/236)	72.69% (181/249)
Hypertension	74.49% (616/827)	74.63% (606/812)
Hypercholesterolemia	33.25% (275/827)	35.84% (291/812)
Hyperlipidemia	54.90% (454/827)	54.06% (439/812)
Chronic Obstructive Pulmonary Disease	9.67% (80/827)	10.71% (87/812)
Kidney Disease w/dialysis	0.12% (1/827)	0.00% (0/812)
Kidney Disease w/o dialysis	10.76% (89/827)	11.95% (97/812)
Renal Insufficiency	0.48% (4/827)	0.37% (3/812)
Peripheral Artery Disease	5.68% (47/827)	6.90% (56/812)
Arrhythmia	11.97% (99/827)	13.67% (111/812)
Atrial Fibrillation/Flutter	3.39% (28/827)	3.20% (26/812)
History of Cancer	14.15% (117/827)	15.02% (122/812)

Baseline ischemic status was similar between the treatment and control groups with no significant differences in distribution of ischemic symptoms as presented in **Table 13**.

Table 13. Ischemic Status at Baseline

Ischemic Status	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)
Angina Status		
Asymptomatic/Free of Symptoms	21.31% (176/826)	20.57% (167/812)
Silent Ischemia	3.63% (30/826)	4.56% (37/812)
Stable Angina	49.52% (409/826)	49.88% (405/812)
Unstable Angina	25.54% (211/826)	25.00% (203/812)
CCS classification		
I	18.09% (74/409)	18.77% (76/405)
II	45.23% (185/409)	47.16% (191/405)
III	31.78% (130/409)	30.37% (123/405)
IV	4.89% (20/409)	3.70% (15/405)
Braunwald classification		
IA	8.70% (18/207)	4.95% (10/202)
IIA	5.31% (11/207)	2.97% (6/202)
IIIA	8.70% (18/207)	7.92% (16/202)
IB	19.81% (41/207)	21.78% (44/202)
IIB	21.74% (45/207)	20.30% (41/202)
IIIB	28.02% (58/207)	32.67% (66/202)
IC	2.42% (5/207)	3.47% (7/202)
IIC	1.93% (4/207)	3.96% (8/202)
IIIC	3.38% (7/207)	1.98% (4/202)

Key Baseline Lesion Characteristics:

Table 14 presents baseline lesion characteristics as interpreted by an independent core lab using quantitative coronary analysis (QCA). In OPTIMIZE patients, mean reference vessel diameter was 2.78 ± 0.50 mm, mean lesion length was 14.57 ± 7.28 mm, and mean percent diameter stenosis was 83%. The target lesion location distribution is generally reflective of patients presenting for PCI with 44% in the LAD, 27% in the LCX, and 28% in the RCA. Approximately 74% of lesions were classified as complex (B2/C).

Table 14. Baseline Lesion Characteristics

Baseline Lesion Characteristics	Svelte DES (N=827 Patients N=1018 Lesions)	XIENCE/Promus DES (N=812 Patients N=970 Lesions)
Number of Target Lesions (Mean±SD (n))	1.27 ± 0.52 (822)	1.22 ± 0.45 (809)
Vessel Location		
LAD	42.93% (437/1018)	45.82% (444/969)
LCX	27.31% (278/1018)	26.52% (257/969)
RCA	29.57% (301/1018)	27.66% (268/969)
LM	0.20% (2/1018)	0.00% (0/969)
Lesion Location		
Proximal	37.43% (381/1018)	39.32% (381/969)
Mid	36.54% (372/1018)	35.50% (344/969)
Distal	22.00% (224/1018)	19.71% (191/969)
Ostial	4.03% (41/1018)	5.47% (53/969)
ACC/AHA Lesion Class		
A	5.70% (58/1018)	5.88% (57/969)
B1	18.96% (193/1018)	22.08% (214/969)
B2	32.22% (328/1018)	31.06% (301/969)
C	43.12% (439/1018)	40.97% (397/969)

Baseline Lesion Characteristics	Svelte DES (N=827 Patients N=1018 Lesions)	XIENCE/Promus DES (N=812 Patients N=970 Lesions)
Calcification		
None/Mild	65.13% (663/1018)	63.26% (613/969)
Moderate	24.66% (251/1018)	25.90% (251/969)
Severe	10.22% (104/1018)	10.84% (105/969)
Bifurcation	22.79% (232/1018)	22.39% (217/969)
Lesion Length (mm)		
Mean±SD (N)	14.88±7.04 (1018)	14.25±7.52 (969)
Reference Vessel Diameter (mm)		
Mean±SD (N)	2.78±0.51 (1018)	2.77±0.50 (969)
Minimal Lumen Diameter (mm)		
Mean±SD (N)	1.00±0.41 (1018)	1.00±0.40 (969)

D. Safety and Effectiveness Results

The primary endpoint was a composite that combined measures of both safety and effectiveness.

Primary Endpoint: The primary endpoint was not met (**Table 15**). Non-inferiority of the primary endpoint of target lesion failure (TLF; cardiac death, target vessel MI, or clinically-driven TLR) 12 months following Svelte DES implantation compared to the Control DES group was not demonstrated.

The 12-month TLF rate was 10.30% in the Svelte DES group compared to 9.49% in the Control DES group. The difference in rates was 0.81% with a two-sided 95% confidence interval (CI) of -2.15% to 3.78%. Because the upper bound of this CI is higher than the pre-specified non-inferiority delta of 3.58%, non-inferiority of the Svelte DES to the Control DES with regard to 12-month TLF was not met.

Table 15. Analysis of Primary Endpoint and Components at 12-Months

	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)	All Patients (N=1639 Patients)	Difference [95% Confidence Interval][1]	Non-Inferiority P-Value[1]
TLF	**10.30% (82/796)**	**9.49% (74/780)**	**9.90% (156/1576)**	**0.81% [-2.15%,3.78%]**	**0.034**
Cardiac Death	0.25% (2/791)	0.26% (2/777)	0.26% (4/1568)	-0.00% [-1.35%,1.34%]	
Protocol-defined TVMI	9.43% (75/795)	8.22% (64/779)	8.83% (139/1574)	1.22% [-1.60%,4.04%]	
Clinically-driven TLR	1.52% (12/789)	1.93% (15/777)	1.72% (27/1566)	-0.41% [-2.06%,1.24%]	

[1] Two-sided 95% confidence interval and non-inferiority p-value for $\pi_{SV} - \pi_C \geq 0.0358$ were calculated from Farrington-Manning test where π_{SV} and π_C are the true 12-month TLF rates for Svelte DES and the combined control group of XIENCE and Promus DESs, respectively.

Cumulative incidence curves for TLF (Kaplan-Meier) from index procedure to 12 months are presented in **Figure 6** below.

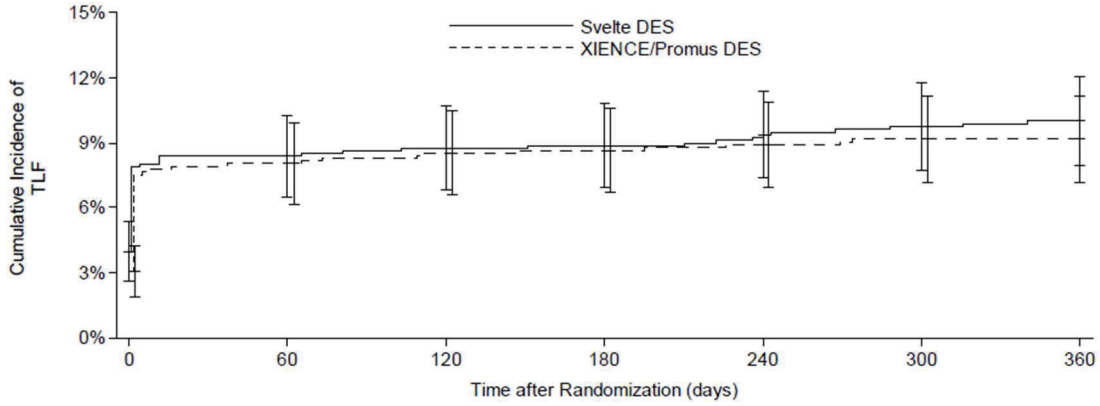

Figure 6: Cumulative Incidence of TLF to 12 Months (Kaplan-Meier)

Examination of Primary Endpoint: The primary endpoint was not met. Additional information is presented below to examine the factors that may have influenced this outcome.

Poolability of the Control DES data:

The two stents comprising the control group (XIENCE and Promus) are considered to have similar performance characteristics and were assumed to be interchangeable during the design of the OPTIMIZE study. To test this assumption, the consistency of results of the primary endpoint across the two control stents was assessed using a prespecified analysis of the primary endpoint separately for Svelte DES vs. each of the control DES. When comparing Svelte DES patients with XIENCE DES patients only, the rate of 12-month TLF was 6.57% in the XIENCE DES group (N=563). The difference in rates was 3.79% with two-sided 95% CI of 0.82% to 6.75%. When comparing Svelte DES patients with Promus DES patients only (N=190), the rate of 12-month TLF was 17.89% in the Promus DES group and the difference in rates was -7.54% with two-sided 95% CI of 12.33% to 2.75%. Additional prespecified consistency analyses using a logistic regression model and Cox proportional hazards regression model identified the type of control DES to be a statistically significant predictor of 12-month TLF, indicating the primary endpoint rates were not homogenous between the two control DES groups. As discussed below, this unexpected difference between the control stents is explained by an imbalance in the biomarkers used to adjudicate TVMI and does not reflect a true difference in performance.

Potential Role of Biomarkers

While cardiac death and TLR were similar and at the low end of the expected range across randomized treatment groups, rates of TVMI were higher than the expected rate of 5% (9.4% Svelte DES vs 8.2% control DES), with 90% of all TVMI occurring peri-procedurally. TVMI varied widely by biomarker used for detection but was similar across treatment groups, although the Promus DES group unexpectedly displayed far higher rates of TVMI than the XIENCE DES group (16.9% vs 5.3%). Per protocol definition, TVMI was preferentially assessed using CK-MB, then total CK, with troponin allowed when CK-MB or total CK was not available. Because troponin is known to be a more

sensitive marker, the percentage of patients evaluated using each biomarker was assessed as follows:

- CK-MB was used in 837 patients (53%); 25 (3.0%) met criteria for MI (>3X ULN);
- Total CK was used in 331 patients (21%); 3 (0.9%) met criteria for MI (>2X ULN);
- Troponin I was used in 335 patients (21%); 104 (31%) met criteria for MI (>3X ULN);
- Troponin T was used in 63 patients (4%); 6 (9.5%) met criteria for MI (>3X ULN).

Troponin I or troponin T was used to diagnose TVMI in 25% of all study patients; this group contributed 80% of all protocol-defined TVMI observed. The rates of MI in EVOLVE II were used to set the expected MI rates for OPTIMIZE. However, although both studies preferentially assessed MI using CK-MB, troponin use in OPTIMIZE was far higher – 25% vs 1% – reflecting the increased use of troponin in clinical practice since the EVOLVE II study was conducted.

The incidence of TVMI within the control DES group varied by DES (XIENCE, 5.3% vs. Promus, 17.2%). Retrospective analysis revealed that this difference was driven by biomarker type used to identify MI. Specifically, a high enrolling study site only used troponin assays and Promus DES as the control device and had a 12-month protocol-defined TVMI rate of 44.9% (40.9% Svelte DES vs. 48.9% control DES [Promus]) for the study. This one site resulted in the diagnosis of 22 of the 59 peri-procedural MIs in the control DES group and is also responsible for the statistical heterogeneity observed between the two control stents.

Post-hoc Exploratory Analyses: Unexpectedly high rates of TVMI in both treatment groups appeared driven by the increased use of troponin compared to EVOLVE II, coupled with a low threshold MI study definition, effectively underpowering the study. Rates of TLF in both treatment groups exceeded the estimates used to power the study and the analysis for non-inferiority did not reach the required pre-specified level of statistical significance (p=0.025). The fixed non-inferiority margin (NIM) of 3.58% that was chosen based on the TLF estimate of 6.5% resulted in loss of statistical power. For this reason, the applicant conducted additional post-hoc analyses to assess non-inferiority of the Svelte DES to the control DES. Please note that these statistics should be interpreted with caution as these analyses were not pre-specified. They are presented here to add additional context to the approval decision.

Relative Risk Analysis

The OPTIMIZE study statistical analysis plan specified an absolute/fixed non-inferiority margin of 3.58%. Because TLF rates in both arms were higher than estimated, many more patients would have needed to be enrolled in the study for adequate statistical power to demonstrate non-inferiority. To examine whether using a relative margin would have changed the study outcome, a relative risk (RR) assessment was conducted. This

analysis compared the maximum RR estimate established during study design (TLF estimate + NIM/TLF estimate [(6.5+3.58)/6.5=1.55]) with that observed in the OPTIMIZE study (RR=1.09, 95% CI [0.81-1.46]). Had the OPTIMIZE study been designed with a relative margin, non-inferiority of the Svelte DES compared with the control DES for 12-month TLF would have been demonstrated (P_{NI}=0.009).

Increased Troponin Assumption Analysis

When the OPTIMIZE study was designed, the assumed TLF rate was based on data where CK-MB or total CK was used to assess 99% of patients; however, during the actual trial 25% of patients were assessed using the more sensitive troponin marker. To examine whether an assumed TLF rate based on contemporary biomarker use would have changed the study outcome, a new assumed literature-derived TVMI rate was estimated based on diagnostic assessment using CK-MB or total CK in 75% and troponin in 25% of study patients. MI diagnosis based on CK-MB >3X ULN was therefore estimated at 4-7% and MI diagnosis based on troponin >3X ULN was estimated at 15-20%. In this analysis, the assumed TLF rate was 10.5% (95% CI 8.75%-12.25%) with an updated absolute NIM of 4.37% chosen to maintain 80% statistical power. This analysis demonstrated that had the OPTIMIZE success criteria accounted for increased troponin use, non-inferiority of the Svelte DES compared with the control DES for 12-month TLF would have been demonstrated (P_{NI}=0.010).

Alternative MI Definitions Analyses

The MI definition used in the OPTIMIZE study was relatively sensitive compared to other contemporary definitions. To examine whether alternative definitions of MI would have changed the study outcome, analyses for non-inferiority of 12-month TLF using the SCAI and 4th Universal definitions of MI, which take into account and accommodate troponin levels used in the assessment of peri-procedural MI, were performed. An independent CEC separately adjudicated all biomarker values through 12 months under the SCAI and 4th Universal definitions of MI.

Applying the SCAI definition of MI, 12-month TLF was 3.66% and 3.33% for the Svelte DES and Control DES groups, respectively. Applying the 4th Universal definition of MI, 12-month TLF was 4.04% and 2.95% for the Svelte DES and Control DES groups, respectively. Assuming the CEC was able to make accurate post-hoc adjudications, if the OPTIMIZE trial had used either the SCAI or 4th Universal definitions of MI, non-inferiority of the Svelte DES compared with the Control DES would have been demonstrated.

All post-hoc analyses are summarized in **Table 16**.

Table 16. Post-hoc Assessments of Non-Inferiority of 12-Month TLF

OPTIMIZE Study Endpoint Analysis	Svelte DES (N=827 Patients)	Control DES (N=812 Patients)	Non-Inferiority	Difference or Relative Risk [95% Confidence Interval] [1]	Non-Inferiority P value[1]
TLF: MI per protocol definition	10.30% (82/796)	9.49% (74/780)	Absolute Margin 3.58%	0.81% [-2.15%, 3.78%]	0.034
1) TLF: Protocol-defined MI with relative NIM	10.30% (82/796)	9.49% (74/780)	Relative Margin 1.55%	1.09% [0.81%, 1.46%]	0.009

2)	TLF: Protocol-defined MI with troponin-adjusted absolute NIM	10.30% (82/796)	9.49% (74/780)	Absolute Margin 4.37%	0.81% [-2.17%, 3.79%]	0.010
3)	TLF: MI per SCAI definition	3.66% (29/793)	3.33% (26/780)	Absolute Margin 3.58%	0.32% [-1.64%, 2.29%]	<0.001
4)	TLF: MI per 4th Universal definition	4.04% (32/793)	2.95% (23/779)	Absolute Margin 3.58%	1.08% [-0.85%, 3.01%]	0.006

[1] Two-sided 95% confidence interval and non-inferiority p-value were calculated from Farrington-Manning test.

1. Safety Results

The analysis of safety was based on the ITT cohort of 1639 patients available for the 12-month evaluation. Key safety outcomes are presented in **Table 17**. Adverse events are reported in Tables 18 and 19.

Safety endpoint rates were very similar across treatment groups. ARC definite/probable stent thrombosis was very low, occurring in 3 patients in both treatment groups. The only endpoint that numerically favored the control group was TVMI; this difference is relatively slight.

Table 17. Summary of Safety Endpoints

Event	Svelte DES (n=827)	XIENCE/Promus DES (n=812)
IN-HOSPITAL EVENTS		
Death	0.00% (0/822)	0.00% (0/809)
Target Vessel MI	7.91% (65/822)	7.42% (60/809)
12-MONTH EVENTS		
Death	0.75% (6/795)	1.15% (9/783)
Cardiac death	0.25% (2/791)	0.26% (2/777)
Non-cardiac death	0.50% (4/793)	0.90% (7/781)
Target Vessel MI	9.43% (75/795)	8.22% (64/779)
STENT THROMBOSIS (ARC DEFINITE/PROBABLE)		
Any, all timepoints	0.38% (3/791)	0.39% (3/776)
Acute (≤24 hours)	0.12% (1/822)	0.12% (1/809)
Subacute (>24 hours, ≤30 days)	0.12% (1/819)	0.12% (1/808)
Late (> 30 days, ≤ 1 year)	0.13% (1/790)	0.13% (1/777)

Adverse effects that occurred in the PMA clinical study:

Adverse events that occurred in the OPTIMIZE study are presented below in **Table 18** and **Table 19**. Adverse events were reported by sites using MedDRA preferred terms. Only categories of adverse events occurring at a rate of ≥1% in either treatment group are reported. No CEC-adjudicated unanticipated adverse device effects were reported during the course of the study.

There were a total of 1331 adverse events reported in 536 patients in the Svelte DES group, compared to a total of 1318 adverse events reported in 520 patients in the control DES group through 12 months of follow up. The frequency and nature of adverse events observed in the OPTIMIZE trial were similar to those observed for other drug-eluting stents approved in the US.

Table 18. All Adverse Events Occurring in >1% of Patients

System Organ Class/Preferred Term	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)
Any Adverse Event to 360 Days	**64.81% (536/827)**	**64.04% (520/812)**
Blood and lymphatic system disorders	**0.60% (5/827)**	**2.09% (17/812)**
Anaemia	0.48% (4/827)	1.35% (11/812)
Cardiac disorders	**31.20% (258/827)**	**29.93% (243/812)**
Angina pectoris	6.65% (55/827)	8.87% (72/812)
Angina unstable	3.26% (27/827)	2.83% (23/812)
Arrhythmia	5.08% (42/827)	2.46% (20/812)
Chest pain	4.59% (38/827)	3.94% (32/812)
Coronary artery dissection	7.74% (64/827)	5.79% (47/812)
Coronary artery restenosis	0.73% (6/827)	1.23% (10/812)
Dizziness	3.14% (26/827)	3.20% (26/812)
Myocardial infarction	2.06% (17/827)	2.96% (24/812)
Endocrine disorders	**0.97% (8/827)**	**2.09% (17/812)**
Diabetes mellitus	0.60% (5/827)	1.35% (11/812)
Eye disorders	**1.69% (14/827)**	**1.23% (10/812)**
Gastrointestinal disorders	**8.71% (72/827)**	**8.62% (70/812)**
Abdominal pain	1.93% (16/827)	1.60% (13/812)
Diarrhoea	0.73% (6/827)	1.85% (15/812)
Gastrointestinal haemorrhage	1.09% (9/827)	0.99% (8/812)
Nausea	0.97% (8/827)	1.35% (11/812)
General disorders and administration site conditions	**12.33% (102/827)**	**15.27% (124/812)**
Administration site haematoma	2.18% (18/827)	4.56% (37/812)
Administration site pain	0.36% (3/827)	1.11% (9/812)
Adverse drug reaction	1.93% (16/827)	1.85% (15/812)
Chest pain	1.81% (15/827)	2.22% (18/812)
Fatigue	2.42% (20/827)	2.34% (19/812)
Oedema peripheral	1.57% (13/827)	1.85% (15/812)
Hepatobiliary disorders	**1.45% (12/827)**	**0.62% (5/812)**
Infections and infestations	**4.47% (37/827)**	**3.82% (31/812)**
Upper respiratory tract infection	1.33% (11/827)	0.49% (4/812)
Injury, poisoning and procedural complications	**5.68% (47/827)**	**6.28% (51/812)**
Plaque shift	1.21% (10/827)	1.23% (10/812)
Investigations	**4.35% (36/827)**	**4.56% (37/812)**
Myocardial necrosis marker increased	1.93% (16/827)	2.09% (17/812)
Metabolism and nutrition disorders	**0.85% (7/827)**	**1.97% (16/812)**
Musculoskeletal and connective tissue disorders	**10.88% (90/827)**	**9.73% (79/812)**
Arthralgia	1.33% (11/827)	1.72% (14/812)
Back pain	1.57% (13/827)	1.23% (10/812)
Myalgia	2.66% (22/827)	1.72% (14/812)
Pain in extremity	2.30% (19/827)	1.72% (14/812)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0.73% (6/827)**	**1.48% (12/812)**
Nervous system disorders	**8.34% (69/827)**	**5.67% (46/812)**
Cerebrovascular accident	1.09% (9/827)	0.62% (5/812)
Headache	1.69% (14/827)	1.23% (10/812)
Syncope	1.81% (15/827)	0.74% (6/812)
Psychiatric disorders	**1.09% (9/827)**	**1.48% (12/812)**
Renal and urinary disorders	**4.72% (39/827)**	**4.68% (38/812)**
Urinary tract infection	1.33% (11/827)	1.35% (11/812)
Reproductive system and breast disorders	**0.97% (8/827)**	**1.11% (9/812)**
Respiratory, thoracic and mediastinal disorders	**14.75% (122/827)**	**14.66% (119/812)**
Dyspnoea	5.20% (43/827)	6.28% (51/812)
Epistaxis	1.93% (16/827)	1.11% (9/812)

System Organ Class/Preferred Term	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)
Non-cardiac chest pain	4.72% (39/827)	4.43% (36/812)
Skin and subcutaneous tissue disorders	**8.10% (67/827)**	**7.39% (60/812)**
Contusion	1.33% (11/827)	1.60% (13/812)
Skin infection	3.51% (29/827)	2.83% (23/812)
Surgical and medical procedures	**1.45% (12/827)**	**2.46% (20/812)**
Vascular disorders	**8.95% (74/827)**	**8.00% (65/812)**
Hypertension	1.93% (16/827)	1.72% (14/812)
Hypotension	1.69% (14/827)	1.97% (16/812)

A summary of serious adverse events is presented below in Table XX. A serious adverse event either resulted in death, was life-threatening, required inpatient hospitalization or caused prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or required intervention to prevent permanent impairment or damage. Serious adverse events were reported using MedDRA preferred terms. Only serious adverse events occurring at a rate of ≥1% in either treatment group are reported.

There were a total of 319 serious adverse events reported in 207 patients in the Svelte DES group, compared to a total of 313 serious adverse events reported in 196 patients in the control DES group. Of these, 60 events were reported as related or possibly related to the Svelte device or index procedure, while 55 events were reported as related or possibly related to the control device or index procedure.

Table 19. All Serious Adverse Events Occurring in >1% of Patients

System Organ Class/Preferred Term	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)
Any Serious Adverse Event	**25.03% (207/827)**	**24.14% (196/812)**
Cardiac disorders	**11.73% (97/827)**	**12.56% (102/812)**
Angina pectoris	1.45% (12/827)	2.71% (22/812)
Angina unstable	1.81% (15/827)	2.59% (21/812)
Arrhythmia	2.30% (19/827)	0.74% (6/812)
Coronary artery dissection	1.09% (9/827)	0.49% (4/812)
Myocardial infarction	1.69% (14/827)	1.85% (15/812)
Gastrointestinal disorders	**2.42% (20/827)**	**2.34% (19/812)**
General disorders and administration site conditions	**1.21% (10/827)**	**1.85% (15/812)**
Injury, poisoning and procedural complications	**1.09% (9/827)**	**1.11% (9/812)**
Musculoskeletal and connective tissue disorders	**1.45% (12/827)**	**1.48% (12/812)**
Nervous system disorders	**3.02% (25/827)**	**1.60% (13/812)**
Renal and urinary disorders	**1.33% (11/827)**	**1.23% (10/812)**
Respiratory, thoracic and mediastinal disorders	**2.90% (24/827)**	**2.96% (24/812)**
Non-cardiac chest pain	1.09% (9/827)	1.23% (10/812)
Vascular disorders	**3.26% (27/827)**	**1.85% (15/812)**

2. Effectiveness Results

The analysis of effectiveness was based on the ITT cohort of 1639 evaluable patients at the 12-month time point. Key effectiveness outcomes are presented in **Table 20**.

Device success was analyzed per lesion and defined as attainment of <30% final residual stenosis of the target lesion using only the randomized stent. Lesion success was also analyzed per lesion and defined as attainment of <30% final residual

stenosis of the target lesion using any stent, with or without other interventional devices. Procedure success was analyzed per patient and defined as lesion success and no in-hospital MACE. Acute success rates, TLR, and TVR were very similar in both study groups.

Table 20. Summary of Effectiveness Endpoints

Event	Svelte DES (n=827 Patients N=1044 Lesions)	XIENCE/Promus DES (n=812 Patients N=990 Lesions)
ACUTE SUCCESS		
Device Success	95.40% (995/1043)	95.24% (941/988)
Lesion Success	99.33% (1036/1043)	99.09% (979/988)
Procedural Success	91.35% (750/821)	91.57% (739/807)
IN-HOSPITAL EVENTS		
Clinically-indicated TLR	0.36% (3/822)	0.37% (3/809)
Clinically-indicated TVR	0.36% (3/822)	0.49% (4/809)
12-MONTH EVENTS		
Clinically-indicated TLR	1.52% (12/789)	1.93% (15/777)
Clinically-indicated TVR	3.67% (29/790)	3.47% (27/778)

Angiographic and IVUS Substudy: According to the protocol, the first 150 patients were to be included in the angiographic sub-study and undergo additional angiographic evaluation at 12 months, with the first 60 additionally undergoing IVUS at baseline and 12 months. However, the sub-study was not fully enrolled, with a total of 132 ITT patients (69 Svelte DES and 63 control DES). Of these, a total of 65 patients (33 Svelte DES and 32 control DES) made up the IVUS cohort. Baseline characteristics were similar between treatment groups with the exception of diabetes, which was more frequent in the Svelte DES group compared with the Control DES group (11.6% vs. 1.6%). Analysis of the angiographic primary endpoint of 12-month in-stent LLL was carried out on all angiographic sub-study patients with available angiograms at both the index procedure and at 12 months.

Angiographic sub-study results are presented below in **Table 21**. The primary endpoint of the sub-study was met. Per ITT analysis, at 12 months, in-stent LLL of the Svelte DES was noninferior to the control DES (all control patients in the angiographic cohort received XIENCE). The upper one-sided 95% CI of 0.19 mm was lower than the delta for non-inferiority (0.20 mm).

While most outcomes were similar between treatment groups, a trend in favor of the control DES was noted for in-segment late loss and both in-stent and in-segment binary restenosis. Review of the data showed that the greater prevalence of diabetic patients in the Svelte group likely accounted for these outcome differences. All other angiographic and IVUS measurements were similar between groups with the exception of incomplete stent apposition assessed by IVUS post-procedure (14.3% and 40.7%) and at 12 months (0.0% and 15.4%) in the Svelte DES and control DES groups, respectively.

Table 21. Angiographic and IVUS Sub-Study Endpoints

Angiographic Endpoints	Svelte DES (n=69 Patients N=88 Lesions)	XIENCE DES (n=63 Patients N=74 Lesions)	Difference [Upper One-sided 95% CI]
Substudy Primary Endpoint In-stent Late Lumen Loss	0.29 ± 0.33 mm	0.21 ± 0.41 mm	0.08 mm [0.19 mm]
In-Segment Late Loss	0.27 ± 0.39 mm	0.15 ± 0.47 mm	0.11 mm [0.26 mm]
In-Stent Minimal Lumen Diameter	2.45 ± 0.59 mm	2.47 ± 0.56 mm	-0.02 mm [0.18]
In-Segment Minimum Lumen Diameter	2.37 ± 0.61 mm	2.39 ± 0.53 mm	-0.03 mm [0.17]
In-Stent Percent Diameter Stenosis	13.62 ± 14.04%	12.58 ± 14.71%	1.03% [5.89%]
In-Segment Percent Diameter Stenosis	17.14 ± 12.12%	15.37 ± 13.35%	1.70% [6.39%]
In-Stent Binary Restenosis	4.11% (3/73)	1.59% (1/63)	2.52% [8.02%]
In-Segment Binary Restenosis	5.48% (4/73)	1.59% (1/63)	3.89% [9.96%]
IVUS Endpoints	**Svelte DES (n=33 Patients N=37 Lesions)**	**XIENCE DES (n=32 Patients N=33 Lesions)**	**Difference [95% CI]**
Mean Plaque Burden (% Area)			
Procedure	49.37 ± 7.71 (28)	49.35 ± 5.83 (27)	0.01 [-3.59, 3.62]
12 Months	57.07 ± 6.98 (29)	56.97 ± 5.88 (26)	0.10 [-3.30, 3.50]
In-Stent Obstruction Volume (%)			
Procedure	15.28 ± 11.66 (28)	20.15 ± 16.79 (27)	-4.87 [-12.53, 2.80]
12 Months	18.93 ± 20.21 (25)	22.15 ± 14.77 (24)	-3.22 [-13.10, 6.67]
Incomplete Stent Apposition			
Procedure	14.29% (4/28)	40.74% (11/27)	-26.46% [-49.07%, -3.84%]
12 Months	0.00% (0/29)	15.38% (4/26)	-15.38% [-29.25%, -1.52%]
Resolved	18.18% (4/22)	34.78% (8/23)	-16.60% [-41.87%, 8.67%]
Persistent	0.00% (0/22)	8.70% (2/23)	-8.70% [-20.21%, 2.82%]
Late Acquired	0.00% (0/22)	8.70% (2/23)	-8.70% [-20.21%, 2.82%]

3. Subgroup Analyses

The following pre-operative characteristics were evaluated for potential association with outcomes:

Sex/Gender

To assess for heterogeneity of treatment effect, the OPTIMIZE clinical protocol prespecified analyzing the primary clinical endpoint by sex. The results are presented in **Table 22** below.

Table 22. TLF at 12 Months in Male and Female ITT Patients

Sex	Svelte DES (N=827 Patients)	XIENCE/PROMUS DES (N=812 Patients)	Difference [95% Confidence Interval]
Male	9.62% (56/582)	8.50% (47/553)	1.12% [-2.2%, 4.46%]
Female	12.15% (26/214)	11.89% (27/227)	0.26% [-5.82%, 6.33%]

Although not prespecified, secondary endpoint outcomes for male and female patients from OPTIMIZE are also available (**Table 23**).

Table 23. OPTIMIZE Secondary Endpoints by Sex/Gender

	Svelte DES (N = 827 Patients)		XIENCE/Promus DES (N = 812 Patients)	
	Male (N = 601 Patients)	Female (N = 226 Patients)	Male (N = 575 Patients)	Female (N = 237 Patients)
All death	1.03% (6/582)	0.00% (0/213)	1.26% (7/554)	0.87% (2/229)
Cardiac death	0.35% (2/578)	0.00% (0/213)	0.36% (2/550)	0.00% (0/227)
Target Vessel Q-Wave or non-Q-wave MI	8.78% (51/581)	11.21% (24/214)	7.61% (42/552)	9.69% (22/227)
Clinically-driven TLR	1.56% (9/576)	1.41% (3/213)	1.45% (8/550)	3.08% (7/227)
Clinically-driven TVR	3.47% (20/576)	4.21% (9/214)	3.09% (17/551)	4.41% (10/227)
Stent Thrombosis (ARC definition)	0.35% (2/578)	0.47% (1/213)	0.55% (3/550)	0.44% (1/227)

The overall conclusions of the trial regarding the safety and effectiveness of the Svelte DES can be generalized to males and females.

Age

To assess for heterogeneity of treatment effect, the OPTIMIZE clinical protocol prespecified analyzing the primary clinical endpoint by age (≤75 years and >75 years). The results are presented in **Table 24** below.

Table 24. TLF at 12 Months in ITT Patients ≤75 and >75 Years Old

Age	Svelte DES (N=827 Patients)	XIENCE/PROMUS DES (N=812 Patients)	Difference [95% Confidence Interval]
≤75 years	10.13% (69/681)	10.17% (65/639)	-0.04%[-3.30%, 3.22%]
>75 years	11.30% (13/115)	6.38% (9/141)	4.92% [-2.13%, 11.98%]

Although not prespecified, secondary endpoint outcomes by age from OPTIMIZE are also available (**Table 25**).

Table 25. OPTIMIZE Secondary Endpoints by Age

	Svelte DES (N = 827 Patients)		XIENCE/Promus DES (N = 812 Patients)	
	Age ≤ 75 (N = 707 Patients)	Age > 75 (N = 120 Patients)	Age ≤ 75 (N = 707 Patients)	Age > 75 (N = 120 Patients)
All death	0.44% (3/679)	2.59% (3/116)	1.09% (7/641)	1.41% (2/142)
Cardiac death	0.29% (2/678)	0.00% (0/113)	0.31% (2/637)	0.00% (0/140)
Target Vessel Q-Wave or non-Q-wave MI	9.26% (63/680)	10.43% (12/115)	8.62% (55/638)	6.38% (9/141)
Clinically-driven TLR	1.48% (10/676)	1.77% (2/113)	2.35% (15/637)	0.00% (0/140)
Clinically-driven TVR	3.69% (25/677)	3.54% (4/113)	3.92% (25/638)	1.43% (2/140)
Stent Thrombosis (ARC definition)	0.29% (2/678)	0.88% (1/113)	0.63% (4/637)	0.00% (0/140)

Race and Ethnicity

Although not prespecified, outcomes by race and ethnicity for the OPTIMIZE study are presented in **Table 26**. Of the 1,571 patients completing 12-month follow-up, 1,292 (82.2%) identified as white and 1548 (98.5%) did not identify as Hispanic or Latino. The available race and ethnicity information is too limited to comment on any potential associations.

Table 26. Primary and Secondary Endpoints by Race and Ethnicity

	Svelte DES (N = 827 Patients)						XIENCE/Promus DES (N = 812 Patients)					
Primary & Secondary Endpoints	White (N = 671 Patients)	American Indian or Alaska Native (N = 2 Patients)	Asian (N = 90 Patients)	Black or African American (N = 32 Patients)	Hispanic or Latino (N = 23 Patients)	Native Hawaiian or Pacific Islander (N = 2 Patients)	White (N = 665 Patients)	American Indian or Alaska Native (N = 2 Patients)	Asian (N = 89 Patients)	Black or African American (N = 27 Patients)	Hispanic or Latino (N = 23 Patients)	Native Hawaiian or Pacific Islander (N = 0 Patients)
TLF	10.65% (69/648)	0.00% (0/1)	8.99% (8/89)	3.45% (1/29)	20.00% (4/20)	0.00% (0/2)	9.59% (61/636)	0.00% (0/2)	3.37% (3/89)	32.00% (8/25)	9.09% (2/22)	0.00%(0/0)
Cardiac Death	0.16% (1/645)	0.00% (0/1)	0.00% (0/88)	3.45% (1/29)	0.00% (0/19)	0.00% (0/2)	0.00% (0/633)	0.00% (0/2)	0.00% (0/89)	8.00% (2/25)	0.00% (0/22)	0.00%(0/0)
Target Vessel Q-Wave or non-Q-wave MI	9.89% (64/647)	0.00% (0/1)	6.74% (6/89)	3.45% (1/29)	20.00% (4/20)	0.00% (0/2)	8.49% (54/636)	0.00% (0/2)	3.37% (3/89)	25.00% (6/24)	4.55% (1/22)	0.00%(0/0)
Clinically-driven TLR	1.40% (9/644)	0.00% (0/1)	2.27% (2/88)	0.00% (0/28)	5.26% (1/19)	0.00% (0/2)	1.74% (11/634)	0.00% (0/2)	0.00% (0/89)	12.50% (3/24)	4.55% (1/22)	0.00%(0/0)
All Death	0.77% (5/649)	0.00% (0/1)	0.00% (0/88)	3.45% (1/29)	0.00% (0/19)	0.00% (0/2)	1.10% (7/639)	0.00% (0/2)	0.00% (0/89)	8.00% (2/25)	0.00% (0/22)	0.00% (0/0)
Clinically-driven TVR	3.72% (24/645)	0.00% (0/1)	2.27% (2/88)	7.14% (2/28)	5.26% (1/19)	0.00% (0/2)	2.99% (19/635)	0.00% (0/2)	3.37% (3/89)	12.50% (3/24)	9.09% (2/22)	0.00%(0/0)
Stent Thrombosis (ARC definition)	0.46% (3/646)	0.00% (0/1)	0.00% (0/88)	0.00% (0/28)	0.00% (0/19)	0.00% (0/2)	0.32% (2/633)	0.00% (0/2)	0.00% (0/89)	8.00% (2/25)	0.00% (0/22)	0.00%(0/0)

Diabetic Patients

To assess for heterogeneity of treatment effect, the OPTIMIZE clinical protocol prespecified analyzing the primary clinical endpoint by diabetes status. The results are presented in **Table 27** below. Outcomes were similar across treatment groups.

Table 27. TLF Through 12 Months With and Without Diabetes

Subgroup	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)	Difference [95% Confidence Interval]
Diabetes	10.81% (24/222)	10.97% (26/237)	-0.16% [-5.86%,5.54%]
Non-Diabetes	10.10% (58/574)	8.84% (48/543)	1.26% [-2.17%,4.70%]

Small vs. Large Vessels

To assess for heterogeneity of treatment effect, the OPTIMIZE clinical protocol prespecified analyzing the primary clinical endpoint by vessel size. Patients with at least one target lesion with RVD ≤ the median RVD were placed in the small vessel subgroup. The results are presented in **Table 28** below. Outcomes were similar across treatment groups.

Table 28. TLF Through 12 Months in Small vs. Large Vessels, ITT Population

Subgroup	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)	Difference [95% Confidence Interval]
Vessel Diameter			
Small Vessels	9.88% (42/425)	9.71% (40/412)	0.17% [-3.85%,4.20%]
Large Vessels	10.78% (40/371)	9.24% (34/368)	1.54% [-2.78%,5.87%]

Lesion Length

To assess for heterogeneity of treatment effect, the OPTIMIZE clinical protocol prespecified analyzing the primary clinical endpoint by lesion length. Patients with at least one target lesion with lesion length ≥ the median lesion length were placed in the long lesion subgroup. The results are presented in **Table 29** below. Outcomes were similar across treatment groups.

Table 29. TLF Through 12 Months in Short vs Long Lesions, ITT Population

Subgroup	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)	Difference [95% Confidence Interval]
Lesion Length			
Short Lesions	6.91% (23/333)	6.81% (25/367)	0.09% [-3.66%,3.84%]
Long Lesions	12.74% (59/463)	11.86% (49/413)	0.88% [-3.47%,5.23%]

Delivery Approaches

To assess for heterogeneity of treatment effect, the OPTIMIZE clinical protocol prespecified analyzing the primary clinical endpoint by radial vs femoral access. The results are presented in **Table 30** below. Outcomes were similar across treatment groups.

Table 30. TLF Through 12 Months in Short vs Long Lesions, ITT Population

Subgroup	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)	Difference [95% Confidence Interval]
Access Site			
Radial	9.31% (59/634)	9.25% (57/616)	0.05% [-3.16%,3.27%]
Femoral	14.19% (22/155)	10.32% (16/155)	3.87% [-3.42%,11.16%]

Direct Stenting and Pre-Dilatation Strategies

The OPTIMIZE study additionally evaluated the procedural and clinical effectiveness of the Svelte DES and Control DES using direct stenting (DS) and pre-dilatation strategies. Investigators declared their intended treatment strategy based on vessel and lesion characteristics on the diagnostic angiogram prior to patient randomization. DS was limited by protocol to 30% of total enrollment. At Japanese sites, investigators did not use DS strategies in patients randomized to the Control DES group because this was considered an off label use. A DS treatment strategy was attempted in 30% (491/1,639) of study patients. Of these, 32.4% (159/491) were treated using the SLENDER IDS, 22.2% (109/491) were treated using the DIRECT RX, and 45.4% (223/491) were treated using a control DES. A total of 207 Svelte DES were delivered using the SLENDER IDS, of which 94.7% (196/207) were used with a DS strategy. A total of 888 Svelte DES were delivered using the DIRECT RX, of which 15.0% (133/888) were used with a DS strategy.

Patient demographics and baseline clinical characteristics were similar across treatment strategy groups with the exception of hypercholesterolemia (higher in the DS group) and hyperlipidemia and atrial fibrillation (higher in the pre-dilatation group).

Pre-procedural lesion characteristics including lesion classification, TIMI flow, lesion length, calcification, reference vessel diameter, minimal lumen diameter and % percent diameter stenosis favored the direct stenting group. **Table 31** summarizes pre-procedural lesion characteristics as assessed by an independent core lab:

Table 31. Pre-Procedure Lesion Characteristics

Measure	Direct Stenting (n=491 Patients, n=562 Lesions)	Pre-dilatation (n=1,148 Patients, n=1,426 Lesions)	Difference [95% Confidence Interval]
Vessel Location			
LAD	47.86% (269/562)	42.95% (612/1425)	4.92% [0.05%,9.78%]
LCX	26.16% (147/562)	27.23% (388/1425)	-1.07% [-5.38%,3.23%]
RCA	25.98% (146/562)	29.68% (423/1425)	-3.71% [-8.04%,0.63%]
LM	0.00% (0/562)	0.14% (2/1425)	-0.14% [-0.33%,0.05%]
Lesion Location			
Proximal	37.01% (208/562)	38.88% (554/1425)	-1.87% [-6.59%,2.86%]
Mid	38.26% (215/562)	35.16% (501/1425)	3.10% [-1.62%,7.82%]
Distal	19.75% (111/562)	21.33% (304/1425)	-1.58% [-5.50%,2.34%]
Ostial	4.98% (28/562)	4.63% (66/1425)	0.35% [-1.75%,2.45%]
ACC/AHA Lesion Class			
A	7.83% (44/562)	4.98% (71/1425)	2.85% [0.35%,5.34%]
B1	23.49% (132/562)	19.30% (275/1425)	4.19% [0.13%,8.25%]
B2	31.32% (176/562)	31.79% (453/1425)	-0.47% [-5.01%,4.06%]
C	37.37% (210/562)	43.93% (626/1425)	-6.56% [-11.32%, -1.81%]
Pre-Procedure TIMI Flow			
0	0.00% (0/562)	0.63% (9/1422)	-0.63% [-1.05%, -0.22%]
1	0.00% (0/562)	1.27% (18/1422)	-1.27% [-1.85%, -0.68%]
2	7.47% (42/562)	11.81% (168/1422)	-4.34% [-7.09%, -1.59%]
3	92.53% (520/562)	86.29% (1227/1422)	6.24% [3.42%,9.05%]
Lesion Length (mm)			
Mean±SD (N)	13.47±6.27 (562)	15.01±7.60 (1425)	-1.55 [-2.20, -0.89]
Eccentric	31.32% (176/562)	30.25% (431/1425)	1.07% [-3.44%,5.59%]
Bend (degrees)			
Mean±SD (N)	26.52±25.23 (562)	27.42±26.57 (1425)	-0.90 [-3.41,1.60]
Thrombus	0.36% (2/562)	0.42% (6/1425)	-0.07% [-0.66%,0.53%]
Tortuosity			
None	79.18% (445/562)	75.86% (1081/1425)	3.32% [-0.70%,7.35%]
Moderate	16.37% (92/562)	17.26% (246/1425)	-0.89% [-4.53%,2.74%]
Severe	4.45% (25/562)	6.88% (98/1425)	-2.43% [-4.58%, -0.28%]
Calcification			
None/Mild	70.82% (398/562)	61.61% (878/1425)	9.20% [4.68%,13.73%]
Moderate	23.31% (131/562)	26.04% (371/1425)	-2.73% [-6.90%,1.45%]
Severe	5.87% (33/562)	12.35% (176/1425)	-6.48% [-9.07%, -3.89%]
Reference Vessel Diameter (mm)			
Mean±SD (N)	2.82±0.48 (562)	2.76±0.51 (1425)	0.06 [0.02,0.11]
Minimal Lumen Diameter (mm)			
Mean±SD (N)	1.08±0.38 (562)	0.97±0.41 (1425)	0.10 [0.06,0.14]
Percent Diameter Stenosis (%)			
Mean±SD (N)	61.61±12.46 (562)	64.69±13.10 (1425)	-3.08 [-4.31, -1.84]

Results

Lesion and device success were similar across treatment strategy groups. Procedure success favored the DS group due to lower rates of protocol-defined TVMI in the DS group (in-hospital MACE is a component of procedure success) as seen in **Table 32**.

Table 32. Acute Success - ITT Population

Secondary Endpoints	Direct Stenting (N = 491 Patients N = 573 Lesions)	Pre-dilatation (N = 1148 Patients N = 1461 Lesions)	Difference [95% Confidence Interval]
Lesion Success	99.48% (570/573)	99.11% (1445/1458)	0.37% [-0.39%,1.13%]
Device Success	95.99% (550/573)	95.06% (1386/1458)	0.92% [-1.03%,2.88%]
Procedure Success	96.95% (476/491)	89.09% (1013/1137)	7.85% [5.48%,10.22%]
Direct Stent Strategy Success	93.89% (538/573)	0.00% (0/0)	--

While cardiac death and clinically-driven TLR were similar across treatment strategy groups, an approximate 3-fold increase in protocol-defined TVMI was observed in the pre-dilatation group as seen in **Table 33**. Post-hoc analysis revealed this was a consequence of certain sites exclusively using both predilation strategies and high sensitivity cardiac biomarkers.

Table 33. TLF at 12 Months By Treatment Strategy

Subgroup	Direct Stenting (n=491 Patients)	Pre-dilatation (n=1,148 Patients)	Difference [95% Confidence Interval][1]
TLF	4.19% (20/477)	12.37% (136/1,099)	-8.18% [-11.67%,-4.70%]
Cardiac Death	0.00% (0/476)	0.37% (4/1,092)	-0.37% [-2.12%,1.38%]
Protocol-defined TVMI	3.56% (17/477)	11.12% (122/1,097)	-7.56% [-10.91%, -4.21%]
Clinically-driven TLR	1.47% (7/476)	1.83% (20/1,090)	-0.36% [-2.44%,1.71%]

To examine potential differences between the Svelte DES and Control DES, 12-month TLF and component outcomes in DS and pre-dilatation subgroups were prespecified in the OPTIMIZE protocol and assessed as seen in **Table 34.** TLF Through 12 Months in DS vs Pre-dilatation, ITT Population

Table 34. TLF Through 12 Months in DS vs Pre-dilatation, ITT Population

Procedural Strategy	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)	Difference [95% Confidence Interval]
Direct Stenting	3.42% (9/263)	5.14% (11/214)	-1.72% [-5.40%,1.97%]
Pre-Dilatation	13.70% (73/533)	11.13% (63/566)	2.57% [-1.34%,6.47%]

To validate the performance of both Svelte delivery system models, outcomes when using the SLENDER IDS and DIRECT RX delivery systems using a DS strategy are presented in **Table 35**.

Table 35. Clinical Outcomes Using DS Strategy by Svelte Delivery System

Clinical Outcome	SLENDER IDS N=159 Patients (187 Lesions)	DIRECT RX N=109 Patients (135 Lesions)
Lesion Success	98.93% (185/187)	100% (135/135)
Device Success	98.40% (184/187)	91.85% (124/135)
Procedure Success	96.86% (154/159)	98.17% (107/109)
Direct Stent Strategy Success	91.98% (172/187)	94.07% (127/135)
TLF	4.46% (7/157)	1.89% (2/106)
Cardiac Death	0.00% (0/157)	0.00% (0/105)
Target Vessel MI	3.82% (6/157)	1.89% (2/106)
Clinically-indicated TLR	2.55% (4/157)	0.00% (0/105)
Stent Thrombosis	0.00% (0/157)	0.00% (0/105)

4. Poolability Analyses

As OPTIMIZE combined patients from Europe, Japan, and the US, the study protocol prespecified that a poolability analysis was conducted to determine if data from these regions were sufficiently homogenous to combine. For the primary endpoint, a logistic regression with treatment, region (US vs. outside the US, or OUS) and their interaction as covariates was employed. Statistical significance (0.15 level) of the interaction term indicates the observed effects are not homogeneous between the regions and may potentially negate poolability of the regions for the primary analysis or require assessment of the endpoint rate adjusting for region variability. Consistency of the treatment effect across regions (US vs. OUS) was established with a p-value for interaction of region and treatment of 0.883, indicating the interaction was non-significant as shown in **Table 36**:

Table 36. Heterogeneity Analysis across Regions: TLF at 12 Months

Region	Svelte DES (N=827 Patients)	XIENCE/Promus DES (N=812 Patients)	Difference [95% Confidence Interval]	P-Value for interaction
Region				0.883
US	15.28% (68/445)	13.90% (61/439)	1.39% [-3.27%,6.04%]	
OUS	3.99% (14/351)	3.81% (13/341)	0.18% [-2.71%,3.06%]	

While the poolability analysis demonstrated that outcomes in the US and OUS were sufficiently homogenous to combine, TLF rates were notably higher in the US compared to OUS. To further examine this issue, baseline patient characteristics were compared between US and OUS patients. As expected, there were a greater concentration of Japanese patients in the OUS group. The US group had a higher mean BMI (30.95 ± 6.11) compared to the OUS group (26.74 ± 4.32), and the OUS group had greater smoking habits. Differences in medical history largely favored the OUS group, which had higher rates of diabetes, hypertension, hyperlipidemia, congestive heart failure, chronic obstructive pulmonary dysfunction, kidney disease, and arrhythmia.

The major difference in outcomes between the US and OUS groups was in peri-procedural MI, which was experienced by 11.8% of US patients (110/933) and only 2.1% (15/706) of OUS patients. Cardiac enzyme biomarker differences again appear to have driven this difference in outcomes, as US investigative sites utilized troponin I or T in 388/933 patients (41.6%), and OUS sites utilized troponin I or T in 167/706 patients (24.9%). Additionally, the ULN used by each site varied, with OUS sites tending to use higher ULNs for troponin assays than US sites.

5. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 473 investigators of which none were full-time or part-time employees of the sponsor and

19 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 19
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

OPTIMIZE was the pivotal trial used to support this PMA. Three additional clinical studies have been conducted outside of the US on the Svelte DES – DIRECT I (first-in-human study), DIRECT II (randomized, controlled trial), and DIRECT III (post-market study). These studies provide additional assurance of device safety and effectiveness and are summarized below.

A. DIRECT I (First-In-Human Feasibility Study)

Device: The device used in this study was an earlier generation version of the fixed-wire system (SLENDER IDS); the stent had a slightly different geometric design (with the same strut thickness) and the delivery system had a different wire tip configuration. The drug coating was the same as the current coating.

Primary Objective: The objective of the DIRECT I study was to assess the safety and clinical performance of the Svelte Drug Eluting Stent-on-a-Wire Coronary Stent System in patients with single de novo coronary artery lesions.

Design: DIRECT I was a prospective, single-arm study. Patients were followed for five years.

Patients enrolled were ≥ 18 years in age with stable or unstable angina pectoris, silent ischemia or clinical evidence of MI undergoing planned percutaneous intervention in a single de novo native coronary lesion. Angiographic inclusion criteria included a reference vessel diameter ≥2.50 and ≤3.5 mm with lesion length of ≤20 mm by visual estimation.

A total of 30 patients in 4 centers in New Zealand were treated with the earlier generation Svelte DES between 2011 and 2012.

Demographics: Average age was 61±11 years. Eighty percent of patients were male and 17% had diabetes; 57% had experienced a prior myocardial infarction.

Baseline lesion characteristics: Mean RVD was 2.7±0.5 mm. Percent diameter stenosis was 81.7±11.6%. Fifty percent of the 30 lesions were type B2/C according to the American College of Cardiology/American Heart Association classification scheme, including 1 true bifurcation lesion. Direct stenting was performed in 77% of patients.

Results:

Safety

By 12 months, one of the 29 patients available for follow up had a non-target vessel MI (3rd Universal Definition was used for this study). There were zero deaths or stent thrombosis events in the 29 patients through five years of follow up.

There were a total of five device or procedure-related (possible, probable, or definite) serious adverse events (SAEs). None of these events were considered unexpected in the context of the trial. These events are listed in **Table 37**.

Table 37. DIRECT I Device or Procedure Related Serious Adverse Events

SAE Description	Relationship to Study Device	Relationship to Study Procedure
Procedural dissection – Grade A	Possible	Definite
Vessel trauma – Grade B dissection	Possible	Definite
Proximal edge dissection on deploying study stent	Possible	Definite
In Stent Restenosis	Definite	No
Chest Pain	Possible	No

Effectiveness

Device, lesion and procedure success rates were 97%, 100%, and 100%, respectively. Two patients required additional devices to attain an acceptable angiographic result. There was one device deficiency reported in which the stent could not be deployed. Post-procedure in-stent diameter stenosis was 10.9 ± 6.37%. All but one patient had deployment of the stent with <20% residual stenosis.

At six months, mean in-stent LLL was 0.22±0.27 mm and mean in-segment LLL was 0.14±0.27 mm. One patient developed binary restenosis. Percent diameter in-stent restenosis was 18±10%. No acquired or persistent stent malapposition was observed at 6 months. Two patients underwent angiographically-driven revascularization at 6 months; one at the target lesion and one proximal to the study stent. No patients experienced clinically-driven TLR through five years.

B. DIRECT II

Device: Same as DIRECT I (earlier generation SLENDER IDS).

Primary Objective: To establish non-inferiority of 6-month in-stent LLL with the Svelte IDS compared with a commercially available DES.

Design: DIRECT II was a prospective, multicenter, randomized trial. Patients were randomized at a 2:1 ratio, Svelte DES: Medtronic Resolute Integrity DES. All patients were followed for five years.

Patients enrolled were eligible for PCI with a target lesion stenosis ≥50% and <100% by visual estimate. Up to 2 coronary lesions located in different major epicardial vessels could be treated though only one lesion, designated as the target lesion, could be treated with the study device. Non-target lesions had to be successfully treated with non-study stent(s) prior to treatment of the target lesion. Patients with recent myocardial infarction (within 72-hours) or left ventricular ejection fraction ≤30% were excluded.

A total of 159 patients from 18 centers in seven European countries were randomized in 2013, with 108 patients assigned to the Svelte DES and 51 to the control DES.

Demographics: Average age of Svelte DES patients was 62.7 ± 9.9; control DES patient average age was 64.2 ± 12.4. Most patients were male (75.9% of Svelte DES and 66.7% of control DES). Diabetes was present in 16.8% of Svelte DES and 21.6% of control DES patients. Patients were well-matched in most baseline demographics, with the exception of the number of current or past smokers (30.8% Svelte DES, 19.6% control DES).

Baseline lesion characteristics: Mean reference vessel diameter was very similar between groups (2.68 ± 0.47 mm Svelte DES, 2.74 ± 0.53 mm control DES). Percent diameter stenosis was also very similar (58.8 ± 11.9% Svelte DES, 60.2 ± 11.3% control DES). There was a trend toward inclusion of more lesions with moderate to heavy calcification in the Svelte DES group (21.7%) than the control DES group (9.8%). Direct stenting was attempted in 91% of procedures.

Results

Safety

There were no deaths at 12 months in either group. TVMI rates were 1.9% (2/108) in the Svelte DES group and 7.8% (4/51) in the control DES group. MI was defined using the 3rd Universal Definition, and all MIs observed in the study were attributed to the target vessel. No stent thrombosis was observed in either group at 12 months. Svelte DES safety endpoint rates remained low through 5 years of follow up. **Table 38** summarizes safety outcomes for the 5 years of follow up.

Table 38. DIRECT II Safety Outcomes Through 5 Years

Outcome	Svelte DES (n=108)	Control DES (n=51)
Death		
1 Year	0.0% (0/108)	0.0% (0/51)
2 Years	0.9% (1/108)	0.0% (0/51)
5 Years	4.6% (5/108)	5.9% (3/51)
Cardiac Death		
1 Year	0.0% (0/108)	0.0% (0/51)
2 Years	0.0% (0/108)	0.0% (0/51)
5 Years	0.0% (0/108)	2.0% (1/51)
TVMI		
1 Year	1.9% (2/108)	7.8% (4/51)
2 Years	1.9% (2/108)	7.8% (4/51)
5 Years	3.7% (4/108)	11.8% (6/51)
ARC Stent Thrombosis (Definite/Probable)		
1 Year	0.0% (0/108)	0.0% (0/51)
2 Years	0.0% (0/108)	0.0% (0/51)
5 Years	0.0% (0/108)	2.0% (1/51)

There were a total of 22 SAEs in 17% (18/108) of patients in the Svelte DES group and 8 SAEs in 14% (7/51) of patients in the control DES group. These events are summarized in **Table 39**.

Table 39. DIRECT II Serious Adverse Events

SAE	Svelte DES (N=108)	Control DES (N=51)
Angina, stable	2	0
Arrhythmia	1	1
Hyperthyroidism	1	0
Gastrointestinal bleeding	1	0
Nausea	1	0
Local infection	0	2
Depression	1	0
Fainting/syncope/vasovagal reaction	1	1
Bronchitis	1	0
Other respiratory	1	0
Arthralgia	1	0
Arthritis	0	1
Back pain	1	0
Renal failure/insufficiency	0	1
Atypical chest pain	1	1
Fever/pyrexia	1	0
Chest pain without cardiac enzyme elevation	1	0
Endometrial carcinoma	1	0
Black-out after drinking wine	1	0
Carotid stenosis	1	0
Silent ischemia	1	0
Claudication	2	0
(Re)stenosis	0	1

Effectiveness

Non-inferiority of the Svelte DES to the control DES was established with 6 -month in-stent late lumen loss of 0.09 ± 0.31 mm (Svelte DES) and 0.13 ± 0.271 mm (control DES), for a mean difference of -0.05 mm (95% CI [-0.16, 0.07], p for non-inferiority <0.0001).

Device failure was 1.9% and 0% in the Svelte DES and control DES groups, respectively, with 37% of operators being first-time users of the Svelte DES. Lesion and procedural success rates between groups were similar (lesion success: 96.3% vs 100; procedural success: 94.4% vs 94.1% for Svelte DES and control DES, respectively).

Significant differences in post-procedural angiographic findings, including smaller acute gain, post-procedural MLD, and % diameter stenosis presented in the Svelte DES group compared with the control DES group. Smaller post-procedure acute gain and MLD for the Svelte DES group was attributed to differences in compliance between the Svelte DES and control DES delivery system balloons. The instructions for use for the device were subsequently revised to clarify that a higher deployment pressure is needed to achieve the same stent diameter as less compliant balloons.

At 6-month follow-up, differences in MLD and % diameter stenosis remained; however, there were no significant differences observed with in-stent LLL or binary restenosis.

Six-month OCT results were available in 22 Svelte DES patients. Neointimal hyperplasia area was 0.89 ± 0.33 mm^2 and neointimal hyperplasia volume obstruction was 11.3%. Malapposed struts were detected in 0.7 ± 1.9% of struts. Average strut coverage was 94.2 ± 9.0%.

At 12 months, clinically-indicated TLR was 1.9% (2/108) in the Svelte DES group and 2.0% (1/51) in the control DES group. Clinically-indicated TVR was 3.7% (4/108) and 3.9% (2/51) in the Svelte DES and control DES groups, respectively. **Table 40** summarizes revascularization rates through 5 years of follow up.

Table 40. DIRECT II Clinically-Driven Revascularization Through 5 Years

Revascularization Rates	Svelte DES (n=108)	Control DES (n=51)
Clinically-driven TLR		
1 Year	1.9% (2/108)	2.0% (1/51)
2 Years	1.9% (2/108)	2.0% (1/51)
5 Years	5.6% (6/108)	2.0% (1/51)
Clinically-driven TVR		
1 Year	3.7% (4/108)	3.9% (2/51)
2 Years	3.7% (4/108)	3.9% (2/51)
5 Years	8.3% (9/108)	5.9% (3/51)

C. DIRECT III

Device: Primarily SLENDER IDS with a small cohort treated with DIRECT RX.

Primary Objective: To evaluate the feasibility of a systematic direct stenting strategy with SLENDER IDS in a commercial setting in an all-comers, real-world population.

Design: The DIRECT III study was a prospective, multicenter, single-arm, post-market observational study conducted after CE Mark certification in Europe. Patients were treated with Svelte DES and followed up for one year.

Patients enrolled were intended to be treated with PCI and implantation of the Svelte DES as part of their standard treatment. Exclusion criteria were minimal and reflected an all-comers population.

A total of 529 lesions in 449 patients were treated with 555 Svelte DES (528 SLENDER IDS and 27 DIRECT RX systems) in 2016-2018. Eleven additional consented patients were treated with another or no DES at the operator's discretion. Patients were treated at 10 sites, nine in the Netherlands and one in the UK.

Demographics: Average age was 64.8 ± 11.0 years. 68.2% of patients were male, and 19.7% had type 2 diabetes. At baseline, 13.3% had no angina, 42.8% had stable angina, and 40.2% had unstable angina.

Baseline lesion characteristics: The mean reference vessel diameter was 3.02 ± 0.42 mm and mean lesion length was 16.3 ± 7.13 mm. Approximately one third of lesions were moderately or severely calcified.

Results: The observational study primary endpoint was TLF at 12 months post-procedure, defined as cardiac death, TVMI, or clinically-indicated TLR by percutaneous or surgical methods. TLF was 3.3% (15/448) at 12 months in the ITT population and 3.2% (14/437) in the modified ITT population (only patients receiving a Svelte DES). The MI definition was the same as that used for OPTIMIZE.

At 12 months, cardiac death was 1.1%, TVMI was 0.9% and TLR was 1.4%. All events assumed worst case scenario (any death not confirmed as non-cardiac, all MIs and any revascularization not confirmed as non-target were counted in TLF). No stent thrombosis was reported in any patient enrolled in the study.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The principal safety and effectiveness information for the Svelte Sirolimus-Eluting Coronary Stent Systems is derived from preclinical studies and from the OPTIMIZE clinical trial.

Preclinical testing performed during the design and development of the Svelte DES confirmed the product design characteristics, specifications and intended use.

The in vitro engineering testing conducted on the stent and delivery systems demonstrate the performance characteristics met the product specifications. The biocompatibility evaluation and in vivo animal studies demonstrated the acute and chronic in vivo performance characteristics of the Svelte DES are safe and acceptable for clinical use. The sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The shelf-life testing has established acceptable performance for the labeled shelf life of two years.

A. Effectiveness Conclusions

The results from the OPTIMIZE trial as designed could not statistically demonstrate that the rate of target lesion failure (a composite endpoint including both safety and effectiveness outcomes) at 12 months in the Svelte DES group was non-inferior to the control XIENCE/Promus DES group (10.3% vs 9.5%). However, no clinically significant differences in performance across study groups were observed in any study endpoint. Unexpectedly high rates of TVMI in both groups in combination with a low-threshold MI definition caused the study to be statistically underpowered. High rates of TVMI were specifically seen at sites using troponin as the peri-procedural MI biomarker. Post hoc

analyses demonstrated that had the OPTIMIZE trial been designed with a relative rather than an absolute noninferiority margin, or with taking into account increased clinical use of troponin to assess MI, or used a different widely accepted PPMI definition (SCAI or 4th Universal Definition), non-inferiority would have been demonstrated.

Other measures of effectiveness were generally in line with expectations for a current generation DES. Clinically-driven TLR was 1.52% at 12 months, compared to 1.93% for the control. Clinically-driven TVR at 12 months was 3.67% vs 3.47%. Revascularization rates remained very similar in both groups after two years. When examining acute success of the stenting procedure, overall measures were also acceptable. Lesion, device, and procedure success rates were high and equivalent in both study groups.

The direct stenting strategy attempted in 268 Svelte DES patients was successful in 92.86% of lesions. Imbalances in lesion types selected for direct stenting make outcome comparisons to pre-dilatation strategies difficult, but the OPTIMIZE trial demonstrated that both the SLENDER IDS and DIRECT RX systems can be used successfully for direct stenting when the operator believes such a strategy to be appropriate.

The totality of the available effectiveness data, including that from the previous DIRECT I-III studies, support the conclusion that the Svelte DES is effective for its intended use.

B. Safety Conclusions

The risks of the Svelte DES are based on non-clinical laboratory and animal studies, as well as data collected in a clinical study conducted to support PMA approval as described above.

No safety signals of concern were identified from a review of serious adverse events and CEC-adjudicated events. Device or procedure-related serious adverse events were of similar type and frequency to those previously reported for other US-approved coronary stents. No CEC-adjudicated unanticipated device-related adverse events occurred during the OPTIMIZE study.

The TLF composite endpoint of the OPTIMIZE trial included two safety outcomes, rates of cardiac death and TVMI at 12 months. The rate of cardiac death was low and numerically equivalent to the control DES group (0.3%). The rate of TVMI was high in both groups (9.4% Svelte DES vs 8.2% control DES), with 90% of all TVMI occurring peri-procedurally. However, the clinical relevance of peri-procedural elevated troponin in the absence of other clinical findings is currently not known. In OPTIMIZE, 87.5% of patients with protocol-defined elevated troponins were discharged without delay post-procedure. A post-hoc analysis requested by FDA did not reveal any clear differences in death, cardiac death, spontaneous MI, or heart failure between OPTIMIZE patients that were assessed with peri-procedural MI and those that were not. The post-hoc analysis conducted by the applicant that re-adjudicated MI events using the SCAI and 4th Univeral definitions found TVMI rates that were much lower in both groups and more similar to expectations.

In addition, the 12-month rate of stent thrombosis according to the ARC definition was very low and similar in both groups (0.38% in Svelte DES vs 0.51% for the control DES group).

Long-term evaluations out to 5 years are ongoing and require additional data collection and analysis. Available data from the DIRECT I-III studies support long--term safety of the Svelte DES. Additionally, 2 year data from OPTIMIZE were available in summary form at the end of the review period; while not the basis for the approval decision, these data provided additional assurance of safety.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the OPTIMIZE clinical study conducted to support PMA approval as described above.

The probable benefits of the Svelte DES are the same as other contemporary DES. Patients treated with the Svelte DES had immediate increases to their coronary luminal diameter that persisted through one year, as demonstrated in the angiographic substudy. The sirolimus coating on the stent prevents restenosis, as evidenced by low clinically-driven target lesion revascularization rates at one year.

The probable risks of the device are also based on data collected in the OPTIMIZE clinical study conducted to support PMA approval as described above. There were no increased device-related risks compared to the control DES group. OPTIMIZE also did not find any procedure-related risks associated with the use of the Svelte DES that would not be expected with any other coronary stent system. Please refer to Section VIII: Potential Adverse Effects of the Device on Health.

Additional factors to be considered in determining probable risks and benefits for the Svelte DES include:

While there was no evidence of increased risk associated with use of the Svelte DES, the lack of trial statistical power to demonstrate statistical noninferiority leads to some remaining uncertainty. Factors mitigating this uncertainty include other supportive data from the DIRECT I-III studies, a history of safe use in countries outside the US, and a post-approval study that will be conducted to ascertain a more precise TVMI rate associated with the use of the Svelte DES.

Another factor to be considered is the availability of alternative treatments. Coronary artery disease can be accompanied by symptomatic chest pain or silent ischemia that affects patients' quality of life. Coronary artery disease is treatable, but if left untreated, the condition can progress to further stenosis within the arteries, increased symptoms, and the need for revascularization. Available treatments for coronary artery disease include medical therapy, PCI, and coronary artery bypass graft surgery. When treatment for coronary artery disease beyond medications and lifestyle changes is warranted, patients often choose stent deployment over surgical revascularization due to shorter recovery times and the less invasive nature of PCI. The risks associated with use of drug eluting

stents are already well established, and in comparison to medical therapy, PCI has been shown to reduce the incidence of angina and increase quality of life.

There are several other coronary DES with similar indications available in the US. When comparing the relative risk ratios of other contemporary coronary DES pivotal trials that have supported approval, the Svelte DES relative risk of 1.09 [95% CI [0.81-1.46]) is similar, and the clinical outcomes in OPTIMIZE (apart from TVMI, as discussed) were all acceptable.

1. Patient Perspective
   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for improving coronary luminal diameter in patients with symptomatic heart disease due to atherosclerotic lesions in native coronary arteries with a reference vessel diameter of 2.25 mm to 4.0 mm and a lesion length of ≤ 34 mm, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Although the OPTIMIZE study did not meet its primary endpoint, the totality of the available data supports the approval decision. Residual uncertainty regarding the true rate of TVMI will be addressed in a post approval study as outlined in the conditions of approval below.

XIV. CDRH DECISION

CDRH issued an approval order on December 13, 2021. The final clinical conditions of approval cited in the approval order are described below.

1. OPEQ Lead PMA Post-Approval Study – Continued Follow-Up of OPTIMIZE Clinical Study. The Office of Product Evaluation and Quality (OPEQ) will have the lead for this clinical study, which was initiated prior to device approval. The OPTIMIZE Clinical Study (G160227/S004) is a single-blind, randomized, active-control, multi-center clinical study which enrolled 1,645 subjects. The OPTIMIZE Clinical Study was designed to compare the safety and efficacy of the Svelte Sirolimus-Eluting Coronary Stent Integrated Delivery System (Svelte DES-IDS) and Svelte Sirolimus-Eluting Coronary Stent Rapid Exchange Delivery System (Svelte DES-RX) to the commercially available Abbott Vascular XIENCE or Boston Scientific Promus Drug-Eluting Coronary Stents (control DES) through 5 years post-index procedure. The primary endpoint is target lesion failure (TLF) at 12 months post-procedure, defined as cardiac death, target vessel myocardial infarction (TVMI, including Q wave and non-Q wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods. You must collect and report clinical outcomes to FDA through 5 years post-procedure on patients enrolled in the OPTIMIZE Clinical Study.

2. OPEQ Lead PMA Post-Approval Study – Svelte Post-Approval Study. The Office of Product Evaluation and Quality (OPEQ) will have the lead for this clinical study, which has not been initiated. The Svelte PAS is a prospective, multicenter, non-randomized study intended to monitor and evaluate the safety and efficacy outcomes of the Svelte DES post-PMA approval of the SLENDER IDS and DIRECT RX systems in a real world setting. The study will enroll approximately 500 subjects with coronary artery disease (CAD) at up to 50 clinical sites, with at least one-half of clinical sites and study subjects from the United States. The primary endpoint for all study subjects enrolled in the Svelte PAS is percentage of subjects with target lesion failure (TLF) at 12 months post-procedure, defined as cardiac death, non-fatal target vessel myocardial infarction (TVMI, including Q wave and nonQ wave) or clinically-driven target lesion revascularization (TLR) by percutaneous or surgical methods. All subjects will require pre-procedure enrollment to ensure pre- and post-procedural cardiac biomarkers are collected. A central core lab will be used in the assessment of cardiac biomarkers. Follow-up contacts post-procedure will be made for clinical assessment at 30 days and 1, 2 and 3 years. There are additionally several secondary endpoints. The final protocol was revised and emailed on November 24, 2021. You must collect and report clinical outcomes to FDA through at least 3 years post-procedure on patients enrolled in the Svelte PAS.

   The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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