# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

| | |
|---|---|
| Device Generic Name: | Drug Coated Balloon (DCB) Percutaneous Transluminal Angioplasty Catheter |
| Device Trade Name: | Chocolate Touch ® Paclitaxel Coated PTA Balloon Catheter |
| Device Product Code: | ONU |
| Applicant's Name and Address: | TriReme Medical, LLC<br>7060 Koll Center Parkway, Suite #300<br>Pleasanton, CA94566 |
| Date of Panel Recommendation: | None |
| Premarket Approval Application (PMA) Number: | P210039 |
| Date of FDA Notice of Approval: | November 4, 2022 |

## II. INDICATIONS FOR USE

The Chocolate Touch® (Paclitaxel Coated PTA Balloon Catheter) is indicated for percutaneous transluminal angioplasty, after appropriate vessel preparation, of *de novo* or restenotic lesions up to 180 mm in length in native femoral or popliteal arteries with reference vessel diameters of 4.0 mm to 6.0 mm.

## III. CONTRAINDICATIONS

The Chocolate Touch® (Paclitaxel Coated PTA Balloon Catheter) is contraindicated for use in:

- Coronary arteries, renal arteries, and supra-aortic/cerebrovascular arteries
- Lesion is unable to be crossed with a guidewire.
- Patients who cannot receive recommended antiplatelet and/or anticoagulant therapy.
- Patients with known allergies or sensitivities to paclitaxel.
- Pregnant or breast-feeding women or women who are intending to become pregnant, or men intending to father children.

## IV. WARNINGS AND PRECAUTIONS

**A signal for increased risk of late mortality has been identified following the use of paclitaxel-coated balloons and paclitaxel-eluting stents for femoropopliteal arterial disease beginning approximately 2-3 years post-treatment compared with the use of non-drug coated devices. There is uncertainty regarding the magnitude and mechanism for the increased late mortality risk, including the impact of future device exposure. Physicians should discuss this late mortality signal and the benefits and risks of available treatment options with their patients.**

Additional warnings and precautions can be found in the Chocolate Touch® (Paclitaxel Coated PTA Balloon Catheter) labeling.

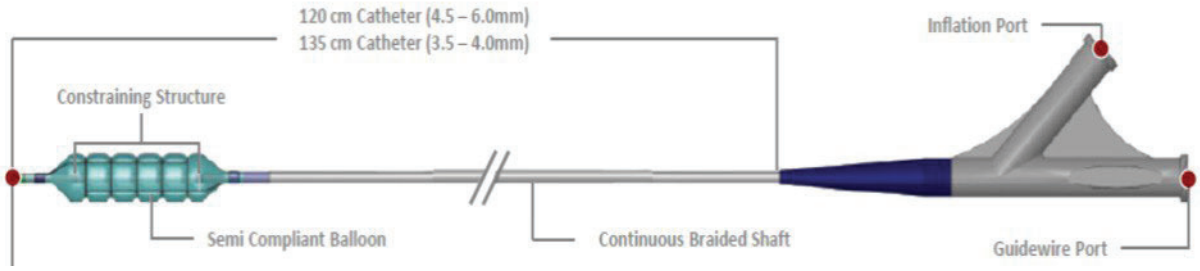
## V. DEVICE DESCRIPTION

The Chocolate Touch® (Paclitaxel Coated PTA Balloon Catheter), hereafter referred to as Chocolate Touch or Chocolate Touch DCB, is a sterile, single-use, over-the-wire (OTW) device/drug combination product comprised of two components, the catheter and the drug coating.

### Catheter Description

The Chocolate Touch® (Paclitaxel Coated PTA Balloon Catheter) is an "over-the-wire" balloon dilatation catheter with a braided shaft and an atraumatic tapered tip. The distal end of the catheter has a semi-compliant balloon that expands to known diameters (refer to compliance chart) at specific pressures. The balloon is constrained by a nitinol constraining structure (CS) which facilitates uniform inflation and fast deflation. Upon deflation, the CS is removed from the vessel along with the balloon catheter. The product family consists of 0.014"and 0.018" systems that are compatible with 0.014"and 0.018" guidewires, respectively. The balloon is available in multiple sizes and contains two radiopaque markers to assist with positioning. Overall catheter lengths range from 120-135 cm. The Chocolate Touch is compatible with 5F to 7F introducer sheaths. (See **Figure 1**)

**Figure 1. The Chocolate Touch Paclitaxel-coated PTA Balloon Catheter**




The Chocolate Touch is available with fifteen (15) total balloon sizes compatible with 5F to 7F introducer sheaths. **Table 1** summarizes the available configurations.

**Table 1. Chocolate Touch Device Configurations**

| Catalogue Number | Description (mm) | Guidewire (in) | Catheter Length (cm) |
|---|---|---|---|
| TUAA-BBB-XXYYY OTW | Diameters (XX): 4.0, 4.5, 5.0, 5.5, 6.0<br>Lengths (YYY): 40, 80, 120 | 0.014, 0.018 (AA) | 120-135 (BBB) |

The 0.014" guidewire compatible catheter is 135cm in length, including 4.0mm diameter balloons of all available lengths (40mm, 80mm, 120mm). The 0.018" guidewire compatible catheter is 120cm in length, including 4.5 – 6.0mm diameter balloons of all lengths (40mm, 80mm, 120mm). The full matrix of balloon sizes evaluated in this PMA submission is summarized in **Table 2**. Product specifications by balloon size are summarized in **Table 3**.

**Table 2. Chocolate Touch Evaluation Matrix**

| | | Balloon Length (mm) | | |
|---|---|---|---|---|
| | | 40 | 80 | 120 |
| Diameter (mm) | 4.0 | × | × | × |
| | 4.5 | × | × | × |
| | 5.0 | × | × | × |
| | 5.5 | × | × | × |
| | 6.0 | × | × | × |

**Table 3. Nominal Pressure and Guidewire and Introducer Sheath Compatibility**

| Balloon Diameter (mm) | Balloon Length (mm) | Nominal Balloon Pressure | Rated Burst Pressure | Guidewire Compatibility | Introducer Sheath |
|---|---|---|---|---|---|
| 4.0 | 40 | 9 atm | 14 atm | 0.014” | 5F |
| | 80 | | | | |
| | 120 | | | | 6F |
| 4.5 | 40 | 8 atm | 12 atm | 0.018” | |
| | 80 | | | | |
| | 120 | | | | |
| 5.0 | 40 | | | | |
| | 80 | | | | |
| | 120 | | | | |
| 5.5 | 40 | | | | |
| | 80 | | | | |
| | 120 | | | | |
| 6.0 | 40 | | | | |
| | 80 | | | | |
| | 120 | | | | 7F |

## Drug Coating Description

The Chocolate Touch DCB’s nominal paclitaxel dose density is 2.95µg/mm$^2$. **Table 4** summarizes the nominal paclitaxel dose for the full family of Chocolate Touch products.

**Table 4. Nominal Paclitaxel Content by Balloon Size**

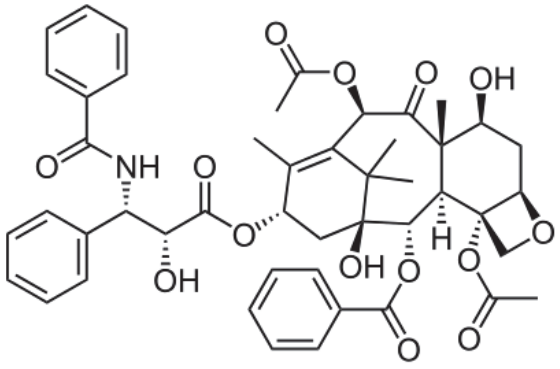
| Diameter/Length | 40 mm | 80 mm | 120 mm |
|---|---|---|---|
| 4.0 mm | 1778mg | 3557mg | 5335mg |
| 4.5 mm | 2001mg | 4002mg | 6002mg |
| 5.0 mm | 2223mg | 4446mg | 6669mg |
| 5.5 mm | 2445mg | 4891mg | 7336mg |
| 6.0 mm | 2668mg | 5335mg | 8003mg |

*Active Pharmaceutical Ingredient (API)- Paclitaxel*

The API of the Chocolate Touch DCB is paclitaxel. The principal mechanism by which paclitaxel inhibits neointimal growth is through the stabilization of microtubules by preventing their depolymerization during the final G2/M phase of cell division. The CAS Registry number of paclitaxel is 33069-62-4. The systematic IUPAC chemical name is (2aR- 2aα,4β,4aβ,6β,9α α

R*,βS*),11α,12α,12bα))-β-(Benzoylamino)- αhydroxybenzenepropanoic acid 6,12b-bis(acetyloxy)-12- (benzoyloxy)- 2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl- 5- oxo-7,11-methano-1H-cyclodeca(3,4)benz(1,2-b)oxet-9-yl ester, and the chemical formula is $C_{47}H_{51}NO_{14}$. The molecular mass of paclitaxel is 853.906 g/mol and has a molecular structure as shown in **Figure 2**.

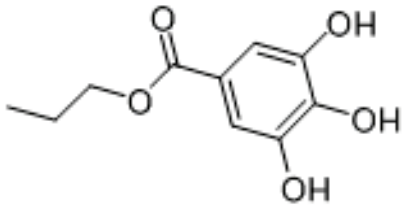
**Figure 2. Molecular Structure of Paclitaxel**




*Excipient – Propyl Gallate*

The Chocolate Touch coating contains, propyl gallate, [3,4,5-trihydroxybenzoate]; CAS #121-79-9 as the excipient. The excipient is an inactive substance that serves to facilitate paclitaxel treatment of the Chocolate Touch device. The molecular mass of propyl gallate is 212.22 g/mol and has a molecular structure as shown in **Figure 3**.

**Figure 3. Molecular Structure of Propyl Gallate**




**Mechanism of Action**

The Chocolate Touch DCB is a PTA catheter with an anti-proliferative drug coating on the distal assembly. As an angioplasty catheter, the primary mode of action is achieved through the mechanical dilatation of the vessel upon inflation. Drug transfer to the vessel wall during the dilatation is a secondary action designed to minimize restenosis.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of femoropopliteal artery atherosclerotic disease, including:

- Non-invasive treatment (risk factor modification, exercise and/or drug therapy),
- Minimally invasive treatment (plain old balloon angioplasty (POBA), endovascular stent, directional atherectomy), and
- Surgical treatment (surgical bypass).

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 Chocolate Touch DCB was available for distribution in the European Union (EU) while holding CE Mark from August 2015 through September 2019. The Chocolate Touch DCB has not been withdrawn from marketing for any reason related to safety or effectiveness. The CE Mark was withdrawn when the notified body left the European Union and stopped servicing medical devices. The Chocolate Touch is not currently available for commercial distribution.

## VIII. POTENTIAL ADVERSE EFFECTS OF DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- Access-site complications
- Allergic reaction to medication, paclitaxel, contrast medium or nitinol
- Amputation
- Aneurysm
- Arterial dissection or perforation
- Arterial rupture
- Arterial spasm
- Arterio-venous fistula
- Bleeding Complications
- Cardiac arrest
- Cardiac arrhythmia
- Death
- Device malfunction or failure
- Emboli (air, tissue, thrombi, material from device(s) used in the procedure)
- Emergency or non-emergency arterial bypass surgery
- Extravasation of contrast media
- Fracture of the guide wire or any component of the device that may or may not lead to device embolism, serious injury or surgical intervention
- Gastrointestinal bleed
- Hemorrhage or hematoma
- Hypotension
- Infection, local or systemic
- Inflammation
- Myocardial infarction or coronary ischemia
- Neurological deficit
- Pain or tenderness
- Peripheral limb ischemia
- Placement of a bail-out stent
- Pseudo-aneurysm
- Radiation exposure
- Reaction to contrast media / medication
- Renal insufficiency or failure
- Respiratory distress or failure

- Restenosis of treated artery or segment
- Sepsis or systemic infection
- Stroke or transient ischemic attack (TIA)
- Surgical repair of vascular access site
- Thrombosis
- Transfusion
- Total occlusion of the peripheral artery
- Vascular complications which may require surgical repair (conversion to open surgery)
- Worsening of peripheral arterial disease

Potential complications of balloon catheterization include, but are not limited to, the following:

- Balloon rupture
- Detachment of a component of the balloon and/or catheter system
- Failure of the balloon to perform as intended
- Failure to cross the lesion.

Potential complications which may be associated with the use of paclitaxel include, but are not limited to:

- Allergic/immunological reaction to paclitaxel
- Alopecia
- Anemia
- Gastrointestinal symptoms (diarrhea, nausea, pain, vomiting)
- Hematologic changes in vessel wall including inflammation, cellular damage, or necrosis
- Myalgia/Arthralgia
- Myelosuppression
- Peripheral neuropathy

There may be other potential adverse events that are unforeseen at this time. For the specific adverse events that occurred in the clinical study please see **Table 16** in the Clinical Study Section **(Section X**) below.

## IX. SUMMARY OF NONCLINICAL STUDIES

A series of non-clinical laboratory studies were performed with the Chocolate Touch DCB. These evaluations included biocompatibility, *in vitro* bench testing, Good Laboratory Practice (GLP) animal studies, analytical testing, stability and shelf life, and sterilization. A summary for each of these evaluations is provided below.

### A. Biocompatibility

Biocompatibility testing for the Chocolate Touch was conducted to support the balloon with the drug coating and the base catheter with no drug coating. For the purpose of these tests, the balloon with the drug coating was categorized as an implant device with permanent blood contact (>30 days), and the base catheter with no drug coating was categorized as an externally communicating device with limited contact duration (<24 hours) with circulating blood. A summary of the biocompatibility testing to support the Chocolate Touch DCB, and results can be found in **Table 5**. The endpoints of sub-acute (sub-chronic) and chronic systemic toxicity,

thrombogenicity, and implantation were evaluated using coated Chocolate Touch DCB as part of in vivo studies conducted to evaluate the safety of the device in a porcine peripheral artery model, as described in Section D, Animal Studies, below. These additional animal studies demonstrated acceptable results when the product was used in a clinically-relevant vascular location.
Chemical characterization and toxicological risk assessments were conducted to support acute, subchronic, chronic systemic toxicity, genotoxicity, and carcinogenicity endpoints.

**Table 5. Summary of Biocompatibility Testing**

| Test Name | Test Description | Coated Balloon | Full Catheter | Results |
|---|---|---|---|---|
| **Cytotoxicity** | ISO MEM Elution Assay with L-929 Mouse Fibroblast Cells | X | X | Non-cytotoxic response for catheter body; acceptable response for the coated balloon* |
| | Direct Contact | X | | Non-cytotoxic |
| **Sensitization** | ISO Guinea Pig Maximization | X | X | Non-sensitizing |
| **Intracutaneous Irritation** | ISO Intracutaneous Reactivity | X | X | Non-irritating |
| **Acute Systemic Toxicity** | ISO Systemic Toxicity | X | X | Non-toxic |
| **Pyrogenicity** | USP Material Mediated Pyrogenicity | X | X | Non-pyrogenic |
| **Hemocompatibility** | Hemolysis (Direct Contact) | X | X | Slightly hemolytic |
| | Hemolysis (Extract Method) | X | X | Slightly hemolytic |
| | Complement Activation | X | X | Not a complement activator |
| **Chemical Characterization** | GC/MS | X | | Extractables do not pose toxicity concerns for the endpoints of carcinogenicity, genotoxicity, and acute/subchronic/chronic systemic toxicity. |
| | ICP | | | |
| | LC/MS | | | |

*Cytotoxic response from the neat extract of the balloon, but considered acceptable after extract dilution and based on acceptable implantation response from the GLP safety study, noted in Section D below.

## B. <u>In Vitro Bench Testing</u>

**Table 6** provides an overview of the In Vitro bench testing supporting the Chocolate Touch PTA Balloon Catheter. The table includes the tests performed, the objective of the tests, the acceptance criteria and the result of each test.

**Table 6. Summary of In Vitro Bench Testing**

| Test | Test Objective | Acceptance Criteria | Pass/Fail |
|---|---|---|---|
| **Balloon Rated Burst Pressure** | Demonstrate the Chocolate Touch PTA Balloon Catheter will not lose pressure at the balloon, shaft, and any seals at pressure less than the labeled RBP | Loss of Pressure < labeled RBP | Pass |
| **Balloon Inflation and Deflation Time** | Demonstrate successful inflation and deflation of Chocolate Touch PTA Balloon Catheter within clinically acceptable time limits | Inflation Time: ≤ 90 seconds<br>Deflation Time: ≤ 90 seconds | Pass |
| **Balloon/Constraining Structure Fatigue** | Demonstrate the ability of the distal assembly (balloon and constraining structure) to withstand repeated inflation-deflation cycles | The Chocolate Touch PTA Balloon Catheter will sustain 20 repeated inflations from 0 atm to the RBP without loss of pressure | Pass |
| **Catheter Bond Strength** | Demonstrate the Chocolate Touch PTA Balloon Catheter meets the catheter bond tensile strength requirements | The smallest outside diameter of tubing portion of test piece shall meet the following:<br>• ≥0.55mm and < 0.75mm shall meet 3N minimum tensile strength<br>• 0.75-1.15mm shall meet 5N minimum tensile strength<br>• 1.15-1.85mm shall meet 10N minimum tensile strength<br>• >1.85mm shall meet 15N minimum tensile strength | Pass |
| **Constraining Structure Bond Test** | Demonstrate the Chocolate Touch PTA Balloon Catheter meets the catheter bond tensile strength requirements | The catheter shall demonstrate that the CS will remain mounted to the catheter under normal use conditions. | Pass |
| **Tip Pull Strength & Tip Configuration** | Demonstrate the Chocolate PTA Balloon Catheter tip meets the configuration requirements and can withstand the tensile forces applied during clinical use | Catheter tips ≥ 3 mm bond shall meet 0.66 lb. (3 N) minimum tensile strength.<br><br>Tip at distal end shall be smooth, tapered, formed, or similarly finished. | Pass |
| **Torque Strength** | Demonstrate the Chocolate PTA Balloon Catheter is able to withstand torque forces applied during clinical use | The catheter will hold a minimum of 3 rotations while the catheter's distal end is not free to rotate | Pass |
| **Flexibility and Kink Test** | Demonstrate the Chocolate PTA Balloon Catheter is able to withstand clinical vessel articulation without kinking | The catheter should not collapse when wrapped around a 10mm radius. curves without kinking in a bench setting or animal model. | Pass |
| **Dimensional & Balloon Profile** | Demonstrate the compatibility of accessory devices with the Chocolate PTA Balloon Catheter through dimensional evaluation of the catheter and balloon profile | Profile shall be ≤ (less than or equal to) 0.075" for a system 0.014" system.<br><br>Profile shall be ≤ 0.085" for a 0.018" system. | Pass |

| Test | Test Objective | Acceptance Criteria | Pass/Fail |
|---|---|---|---|
| **Simulated Use/Delivery** | Demonstrate the functional performance of the Chocolate PTA Balloon Catheter | The catheter shall demonstrate the ability to track over anatomical curves in a bench setting or animal model | Pass |
| **Radiopacity** | Demonstrate the radiopacity of the Chocolate PTA Balloon Catheter | The catheter shall include radiopaque markers and be visible under fluoroscopy | Pass |
| **Balloon Compliance** | Demonstrate the compliance of the various sizes of the Chocolate PTA Balloon Catheter at varying pressures | Balloon diameter vs. pressure (compliance) will be measured and reported on the label. It is desirable that nominal diameter will be achieved at pressure of 6-12 atm. | Pass |
| **Device Interface Compatibility** | Demonstrate the functional performance of the Chocolate PTA Balloon Catheter during simulated use with common accessory devices | Device shall be compatible with<br>• 0.014" guide wires, (desirable range of 4.0mm diameter and up to 120mm in length) or<br>• 0.018" guide wires (desirable range of 4.5-6.0mm diameter and 40-120mm in length)<br>• Appropriately sized introducer sheaths and other commonly used accessories required to complete the procedure. | Pass |
| **Corrosion** | Demonstrate the corrosion resistance of the materials of the Chocolate Touch PTA Balloon Catheter | Balloon catheter will be tested according to ISO 10555-1 "Sterile, single-use intravascular catheters – Part 1: General requirements" | Pass |

## C. Analytical Testing and Coating Characterization

Analytical testing was performed to determine the identity, safety, purity and quality of the drug coating on the Chocolate Touch PTA Balloon Catheter, as described in **Table 7**.

**Table 7. Summary of Analytical Testing and Coating Characterization**

| Test | Test Objective | Acceptance Criteria | Pass/Fail |
|---|---|---|---|
| **Analytical Testing** | | | |
| **Drug Content** | Demonstrate the paclitaxel concentration meets the product specification. | The paclitaxel content shall be within ± 10% of the nominal values for each balloon size. | Pass |

| Test | Test Objective | Acceptance Criteria | Pass/Fail |
|---|---|---|---|
| **Analytical Testing** | | | |
| **Drug Content Uniformity** | Demonstrate the paclitaxel concentration meets the product specification. | Units shall meet uniformity of dosage requirements in USP 905. | Pass |
| **Excipient Density** | Demonstrate the excipient concentration meets the product specification. | The Excipient concentration shall be no higher than 2.00µg/mm$^2$. | Pass |
| **Coating Appearance** | Visually inspect the distal assembly under magnification to determine if product meets appearance specifications. | The coating shall meet visual inspection requirements. | Pass |
| **Coating Identity** | Demonstrate the presence of paclitaxel on the balloon. | HPLC/UV-chromatogram must correspond to that of Paclitaxel. | Pass |
| **Paclitaxel degradation and impurities** | Ensure the Chocolate Touch PTA Balloon Catheter meets the paclitaxel degradation and | The paclitaxel degradation products and impurities concentrations shall meet the specifications. | Pass |
| **Elution Testing** | Ensure the in vitro elution of the Chocolate Touch PTA Balloon Catheter meets the elution specification. | Elution shall meet requirements. | Pass |
| **Particulate Release** | Ensure the Chocolate Touch PTA Balloon Catheter meets the particulate specifications. | Particulate sizes and counts must be within the established limits. | Pass |
| **Residual Solvent** | Ensure the Chocolate PTA Balloon Catheter meets the residual solvent specifications. | Residual solvents shall meet requirements. | Pass |
| **Coating Characterization** | | | |
| **Coating Uniformity (Longitudinal & Circumferential)** | Determine the paclitaxel percentage per each segment of balloon tested. | The catheter shall be characterized for uniformity. | Pass |
| **Particulate Characterization** | Characterize the released particulates, including chemical identity and crystallinity of the Chocolate Touch PTA Balloon Catheter. | The particulates shall be characterized chemical identity and crystallinity. | Pass |
| **Coating, Thickness, Integrity, and Retention** | Characterize the coating thickness and integrity of the Chocolate Touch PTA Balloon Catheter to evaluate the application of a coating and consistency throughout the length and circumference of the device. | The coating thickness, integrity, and retention shall be characterized in a bench setting or animal model. | Pass |

## D. Animal Studies

The following *in vivo* animal testing was conducting in a porcine iliofemoral artery model to evaluate the safety of the Chocolate Touch DCB:

- A GLP pharmacokinetic (PK) swine study was completed evaluating paclitaxel and excipient content in the blood, arterial tissue, downstream tissue, and select organs.
- A GLP safety swine study (1X and 3X) was completed evaluating the effects of Chocolate Touch treatment on local tissue, downstream tissue, and select organs.

All animal studies were conducted in accordance with 21 CFR 58 (Good Laboratory Practices). In addition to the principal endpoints noted for each study, all animals were carefully evaluated for general health (vital signs, behavior, nutritional condition, gait, etc.) and clinical responses to treatment.

A list and description of these animal studies conducted is presented in **Table 8**.

**Table 8. Summary of Animal Studies**

| Study | Animal Model & Count | Local Drug Dose | Size | Duration & Major Endpoints | Endpoints Met? |
|---|---|---|---|---|---|
| **Pharmacokinetic Study of the TriReme Medical Chocolate Touch Drug-Coated Balloon Catheter in Swine Peripheral Arteries** | 72 Domestic Farm Swine | 1X, 3X | 6.0x80mm | Arterial Tissue PK: 1 hr and 1,3,7,14,30,90,18- and 270 days<br>Plasma PK: 5 min, 1, 3, 6, 12, 24 hours, 2, 3, and 7 days<br>Downstream Tissue PK: 1 hr and 1,3,7,14,30,90,180 and 270 days | Yes |
| **Safety Study of the TriReme Medical Chocolate Touch™ Drug- Coated PTA Balloon Catheter in Swine Peripheral Arteries** | 34 Domestic Farm Swine | 1X, 3X or control | 6.0x80mm | Target site histopathology at 30, 90, and 180 days<br>SEM at 7 days<br>Arterial patency angiogram at 30, 90 and 180 days<br>Downstream skeletal muscle tissue histopathology; at 30, 90, and 180 days organ histopathology at 30, 90, and 180 days | Yes |

The preclinical studies conducted demonstrate and confirm the safety of treatment with the Chocolate Touch. The GLP safety evaluation study of the Chocolate Touch DCB demonstrated favorable safety parameters as defined by the following:

- Acute device performance for the Chocolate Touch was comparable to that of the control article (POBA) in terms of preparation, ease of insertion through a guiding sheath,

trackability, pushability, marker band radiopacity, and withdrawal. No thrombus was observed.

- No deleterious effects were observed during the in-life portion of the study demonstrating safety of the device in this model. No animal morbidity or mortality. There were no significant abnormalities in the clinical pathology data.

- The histological assessments of the treated iliofemoral arteries did not reveal any signs of drug-induced vessel toxicity arising from any of the Chocolate Touch treatment groups (1X, 3X). There was no incidence of biologically significant local adverse effects related to the device or the device coating. No excessive neo-intimal formation, medial necrosis, thrombotic occlusions, or aneurysm formation in follow-up studies inclusive of 180 days was present.

- No major angiographic differences were observed between test and control treatment groups. No vessel abnormalities were reported. There was no sign of drug-induced vascular toxicity in any of the study arms. There was no evidence of downstream or systemic adverse effects.

- Histopathology data demonstrated an acceptable embolic load safety margin for the intended therapeutic dose and indicated range of allowable balloon lengths.

The preclinical pharmacokinetic study demonstrated effective drug delivery and uptake into the arterial tissues at the therapeutic dose density (2.95 $\mu g/mm^2$) with no evidence of drug toxicity demonstrated as follows:

- Bilateral administration of Chocolate Touch Paclitaxel Drug-Coated Balloon Catheter at 1X nominal and 3X safety margin dose in porcine peripheral arteries resulted in acceptable acute device performance.

- No deleterious effects were observed during the in-life portion of the study demonstrating safety of the device in this model. No animal morbidity or mortality.

- Paclitaxel pharmacokinetics similar to other paclitaxel coated balloons, with rapid clearance of the novel excipient. The mean paclitaxel concentrations in ancillary and arterial tissues reached levels below quantification by Day 90 at nominal dose and Day 180 for the 3X safety margin dose. Plasma paclitaxel concentrations reached levels below quantification by 48 hrs at nominal dosage.

- The presence of paclitaxel in major organs (e.g., lungs) or local or downstream muscles was not associated with any adverse clinical reactions. Systemic concentrations correlated to the size and number of devices used. No explant abnormalities were noted.

## E. Additional Studies

*Stability and Shelf Life*

The Chocolate Touch Paclitaxel-Coated PTA Balloon Catheter has a 2-year shelf life.

Mechanical testing results demonstrate that the device continues to meet the mechanical/functional performance specifications after 24 months of accelerated aging, which was also confirmed through real time aging.

Finished product stability studies were conducted according to United States Pharmacopeia (USP) and International Conference of Harmonization (ICH) guidelines to establish the shelf life. The testing includes an evaluation of potency, impurities, coating appearance, *in vitro* elution, particulates, and sterility. The product shelf life is supported by the 2-year long term and 6-months accelerated aging stability data.

*Sterilization*

The Chocolate Touch Paclitaxel-Coated PTA Balloon Catheter is sterilized using ethylene oxide sterilization, which has been validated per AAMI/ISO 11135-1:2007. Testing for ethylene oxide residuals was completed and acceptable per ANSI/AAMI/ISO 10993-7:2008 (R) 2021. Results from sterilization studies show the product satisfies a minimum Sterility Assurance Level (SAL) of $10^{-6}$. The amounts of bacterial endotoxin are verified on every lot to be within the specification limit.

## X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish reasonable assurance of safety and effectiveness of percutaneous balloon angioplasty, after pre-dilatation, of de novo and restenotic lesions in native superficial femoral and popliteal arteries with the Chocolate Touch DCB in the USA, Germany, Austria, and New Zealand under IDE # G160085. Data from this clinical study formed the basis of the PMA approval decision. A summary of the study is presented below.

### A. Study Design

Patients were treated between July 26, 2017, and May 26, 2020. The database for this PMA reflected data collected through May 20, 2021 and included 333 patients (313 randomized and 20 roll-in) randomized 1:1 to the Chocolate Touch DCB (n=152) or the control device, the Lutonix 035 Drug Coated PTA Catheter (Lutonix DCB) (n=161). There were 34 investigational sites (28 in the USA, 5 in Europe, and 1 in New Zealand).

The Chocolate Touch Study is a prospective, randomized, multi-center, single-blind study comparing the Chocolate Touch DCB to the Lutonix DCB, for treatment of femoropopliteal arteries in a single limb. Safety oversight of the study was provided by an independent Data Safety Monitoring Board (DSMB). An independent Clinical Events Committee (CEC) adjudicated various study endpoints. Angiographic analysis of all index procedure and re-intervention angiograms was performed by a qualified independent Angiographic Core Laboratory.

1. Clinical Inclusion/Exclusion Criteria

Enrollment in The Chocolate Touch Study was limited to patients who met the following general and angiographic inclusion criteria:

- Minimum of 18 years of age

- Intermittent claudication or ischemic rest pain (Rutherford 2-4)
- Life Expectancy >2 years
- Patient has agreed to follow-up requirements and given informed consent
- Lesion successfully crossed with a guidewire
- Lesion in the SFA or popliteal artery defined as a lesion with a proximal origin >10mm from SFA origin (deep femoral artery) and a distal end above the knee joint (at least 3 cm above bottom of the femur- P1)
- Target Lesion ≥70% stenosis in the SFA or popliteal arteries
- Reference Vessel Diameter (RVD) between 4.0 & 6.0mm and within treatment range of Chocolate Touch to be used 1.1:1 at the Target Lesion
- Target Lesion ≤180mm that consists of no more than two adjacent lesions ≤ 25mm apart) and is able to be completely covered with inflation of no more than two assigned balloons (with minimum of >5mm overlap to the area covered by the first balloon)
  Note: Adjacent or tandem target lesions must be treated as a single lesion
- Angiographic evidence of distal run-off demonstrated by at least one patent tibial vessel without evidence of significant ≥70%) stenosis from origin to ankle
- In-flow vessel without significant stenosis ≥70%) or successful treatment ≤30% residual stenosis with no complications) of a diseased vessel
  Note: treatment of contralateral iliac is permissible

Patients were <u>not</u> permitted to enroll in The Chocolate Touch Study if they met any of the following general or angiographic exclusion criteria:

- Acute limb ischemia, or patient indicated for thrombolytic therapy
- Planned surgical or interventional procedures within 30 days after study procedure
- Non-target lesion concurrent interventions involving a re-entry device, atherectomy, laser, or ablation procedures, the use of a drug eluting stent, or treatment with any other drug coated balloon
- Myocardial infarction or stroke within 30 days prior to the procedure
- Known intolerance to required medications, contrast media that cannot be adequately premedicated, nitinol, or Paclitaxel
- Known impaired Renal Function that could have an impact on contrast tolerance with GFR ≤ 30 ml/min per 1.73 m2 and/or elevated serum creatinine >2.5mg/dL (220μmol/L or on dialysis
- Known bleeding disorder or uncontrolled hypercoagulable disorder
- Non-atherosclerotic lesion (e.g., vasculitis or Berger's disease)
- Female of child-bearing age who is Pregnant or intends to be pregnant during study
- Patient is enrolled in another investigational clinical study or was previously enrolled in this study
- Presence of perforation, dissection (Type D or worse) or other injury in target vessel at time of enrollment
- Severe Calcification at the target lesion (defined as angiographic evidence of dense calcification present on both sides of the vessel wall on two orthogonal views and that extends >50 continuous mm in length)
- Previous bypass graft or stent at target vessel (must be greater than 20mm from target lesion), or iliac stent that cannot permit crossing by the treatment balloon within the introducer sheath
  Note: In-stent restenosis is not allowed

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 30 days, 6, 12, 24 and 36 months with a telephone follow-up at 48- and 60-months post- index procedure. Please see **Table 9** below for the complete procedure and follow-up schedule.

**Table 9. Procedure and Follow-Up Schedule**

| PROCEDURE/TEST | Baseline[1] | Procedure (Day 0) | 1 Month Follow-Up Visit (30 days ± 7 days) | 6 Month Follow-Up Visit (180 days ± 30 days) | 12 Month Follow-Up Visit (364 days ± 30 days) | 24-Month Follow-Up Visit (728 days ± 60 days) | 36-month Follow-Up 1092 days ± 60 days) | 48 Month Phone Call (1446 days ± 60 days) | 60 Month Phone Call 820 days ± 60 days) |
|---|---|---|---|---|---|---|---|---|---|
| **Screening** | | | | | | | | | |
| Informed Consent[2] | ✓ | | | | | | | | |
| General Inclusion / Exclusion Criteria | ✓ | | | | | | | | |
| Angiographic Inclusion / Exclusion Criteria | | ✓ | | | | | | | |
| **Clinical Assessments** | | | | | | | | | |
| Medical History/ Physical Exam[3] | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Laboratory Assessments (creatinine or GFR) | ✓ | | | | | | | | |
| Urine pregnancy test if female[4] | ✓ | | | | | | | | |
| Ankle Brachial Index (ABI) / Toe Brachial Index (TBI) | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Rutherford Clinical Category (RCC) | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Adverse Events Assessment | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| PAD QOL | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| WIQ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Medications: Aspirin / Monotherapy[5] | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Imaging** | | | | | | | | | |
| Angiography | | ✓ | | | | | | | |
| Duplex Ultrasound (DUS) | | | ✓ | ✓ | ✓ | ✓ | ✓ | | |

[1] Standard of care evaluations may be done up to 30 days before the procedure. Protocol-specific exams that are non-standard of care cannot be obtained until after informed consent.

[2] Consent to be obtained within 30 days prior to enrollment.

[3] Medical History is required at baseline only. Refer to applicable Protocol section for physical exam requirements.

[4] Negative pregnancy test within 14 days of enrollment for women of childbearing potential.

[5] DAPT and aspirin are required through 30 days and then continued per physician / institutional standards of care. Aspirin therapy is to be continued indefinitely.

3. Clinical Endpoints

*Primary Safety Endpoint*

The primary safety endpoint assessed the occurrence of Major Adverse Events (MAEs) at 12 months defined as the composite of:

- target-limb-related death
- major amputation of the target limb and
- re-intervention of the target limb

The primary safety endpoint was designed to demonstrate that the 12-month MAE-free rate for the Chocolate Touch DCB treatment group is non-inferior to the Lutonix DCB control group. If both primary endpoints were met (non-inferior safety and effectiveness), then pre-specified hierarchical tests for superiority would be conducted. Superiority for effectiveness would be conducted prior to superiority for safety.

*Primary Effectiveness Endpoint*

True DCB Success at 12 months, defined as primary patency in the absence of clinically driven bail-out stenting (CD-stent), as defined below. A subject with a CD-stent failed this endpoint; subjects that did not have a CD-stent placed were assessed for primary patency for the purposes of determining True DCB Success.

Clinically Driven Bail-Out Stenting (CD-stent): Stents are considered clinically driven when the angiographic core lab determines that a stent was placed after DCB use during the index procedure under the following conditions that were not resolved by prolonged balloon inflation:

- Unresolved flow limiting dissection (Type E or F),
  OR
- Residual lumen diameter stenosis > 50%

A subject with a CD-stent failed the True DCB success endpoint regardless of patency outcomes.

Primary Patency: Subjects achieved primary patency by a combination of duplex ultrasound review and no evidence of CD-TLR prior to the study required 12-month DUS as defined below:

- Duplex Ultrasound Review: A patent target lesion showed a Peak Systolic Velocity Ratio (PSVR) less than 2.4 on DUS review by the DUS core lab
  OR
- Clinically Driven Target Lesion Revascularization (CD-TLR): any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed that was considered clinically driven when both of the following conditions were met:
  - Worsening clinical symptoms in the target limb (based on an ankle-brachial index (ABI) decrease ≥20% or >0.15 compared to maximum early post-procedure ABI or documented increase in Rutherford by at least one class if ABI change was unattainable (independently adjudicated).

- Angiographic core lab adjudication of the revascularization angiogram confirming that the target lesion prior to re-intervention demonstrated diameter stenosis >50%.

This primary effectiveness endpoint was designed to demonstrate that the 12-month true DCB success rate for the Chocolate Touch DCB treatment group is non-inferior to the Lutonix DCB control group. If both primary endpoints were met (non-inferior safety and effectiveness), then pre-specified hierarchical tests for superiority would be conducted. Superiority for effectiveness would be conducted prior to superiority for safety.

*Secondary Endpoints*

The following exploratory secondary endpoints were evaluated:

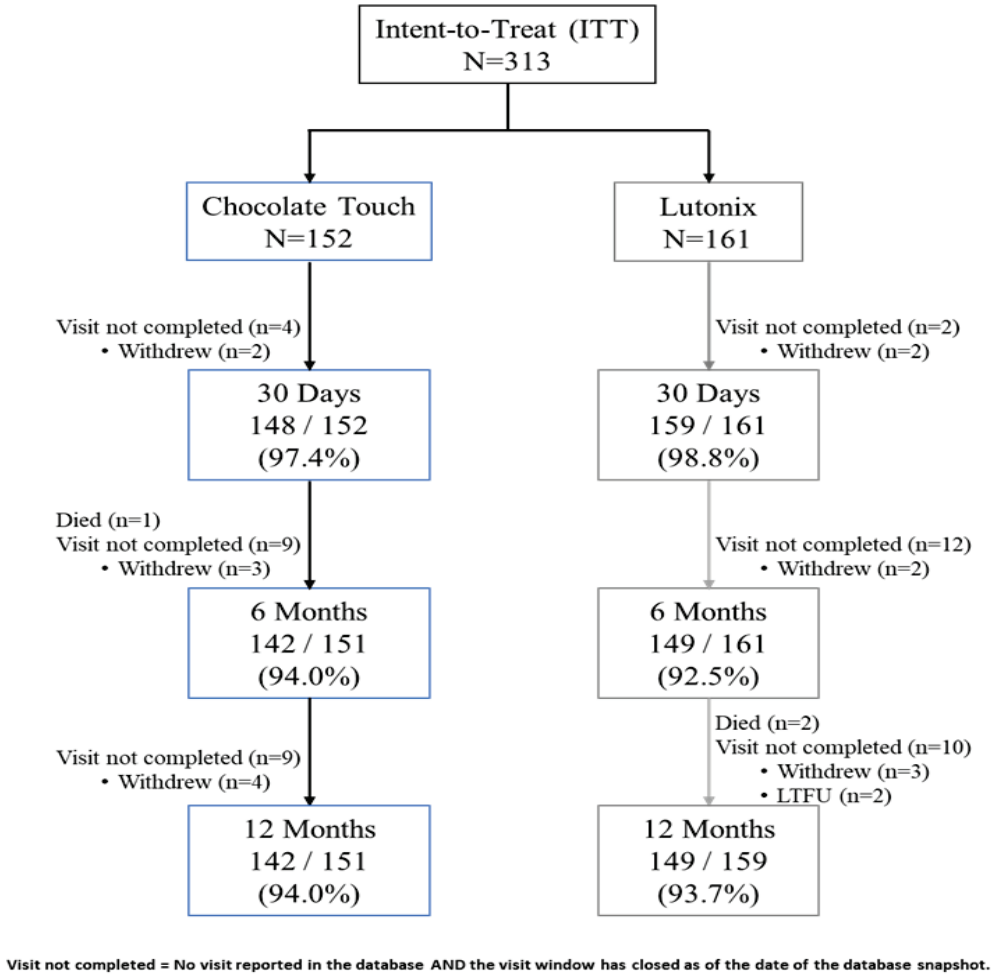
- Technical Success (acute), defined as the ability to deliver and inflate the assigned DCB at the intended target lesion.
- Device Success (acute), defined as the ability to achieve an optimal PTA outcome (≤30% diameter stenosis without the occurrence of a flow-limiting dissection at the target lesion) with the assigned DCB.
- Rate of Clinically Driven Bail-out stenting (CD-stent) (acute), defined as the number of cases in which a CD-stent placement was conducted in accordance with the protocol.
- Rate of Stent Placement (acute), defined as the number of cases in which any stenting was conducted during the index procedure after DCB use.
- Length of Stented Segment (acute)
- Occurrence and severity of target lesion dissection (acute), defined as the number of cases in which dissection occurred
- Rate of Geographic Miss
- Stent-Free DCB Patency, defined as a composite endpoint that required subjects to achieve primary patency in the absence of a stent. Only subjects that did not have a stent placed were assessed for primary patency for the purposes of determining stent free patency.
- Primary Patency at 6, 12, 24, and 36 Months, defined as target lesion restenosis as determined by duplex ultrasound (PSVR < 2.4) and freedom from clinically-driven TLR
- Secondary Patency at 6, 12, 24, and 36 Months as defined by a PSVR less than 2.4 on DUS on review by the DUS Core Lab regardless of the need for TLR.
- Freedom from Clinically Driven TLR at 6, 12, 24, and 36 Months, any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed that was clinically driven.
- Occurrence of target lesion restenosis at 6, 12, 24, and 36 Months.
- Clinical Improvement at 6, 12, 24, and 36 Months as defined by their Rutherford Classification improved by at least one category if ABI improved by at least 20% or 0.15. Results from the Walking Impairment Questionnaire (WIQ) and the Peripheral Artery Disease Specific Quality of Life (PADQOL) Questionnaire were evaluated and assessed for trends.

## B. Accountability of PMA Cohort

At the time of database lock of 313 patients enrolled in the PMA study, 85.3% of

patients had sufficient data to assess the primary effectiveness endpoint at 1 year. Subject follow-up disposition to 12 months is provided in **Figure 4**.

**Figure 4. Subject Disposition Flow Chart up to the 12-Month Follow-up (ITT Analysis Set)**




Visit not completed = No visit reported in the database AND the visit window has closed as of the date of the database snapshot.

Primary effectiveness endpoint accountability at the 12-month post-operative visit is presented in **Table 10**.

**Table 10. Subject Primary Effectiveness Endpoint Accountability Through 12 Months (ITT analysis set)**

| | Chocolate Touch DCB | Lutonix DCB |
|---|---|---|
| **Total Subjects** | 152 | 161 |
| **Not Assessed for primary efficacy (n, [%])** | 15 (9.9%) | 31 (19.3%) |
| **Reason:** | | |
| **Withdrew prior to 12 months** | 4 | 3 |
| **Lost to Follow-up** | 1 | 0 |
| **Missed 12-month visit** | 4 | 9 |
| **Visit outside of window** | 5 | 6 |
| **Completed visit but no DUS** | 1 | 9 |
| **Non-diagnostic DUS** | 0 | 4 |

## C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the US. Baseline demographics, medical history, and risk factors were mostly similar between the Chocolate Touch and Lutonix DCB groups. Data for the Chocolate Touch Study are summarized in **Table 11**. Minor differences were noted for Lutonix DCB subjects who had greater prevalence of coronary artery disease (CAD) and congestive heart failure (CHF) as compared to Chocolate Touch DCB subjects. Post hoc exploratory subgroup analyses were evaluated and it was determined that there was not a significant interaction between the primary outcomes in either of these subgroups (full details included in the Section D.3, **Table 20** and **Table 21)**.

**Table 11. Baseline Demographics and Medical History**

| Parameter | Chocolate Touch DCB | Lutonix DCB | P-value[1] |
|---|---|---|---|
| **Age** | 70.0 ± 9.7 (152) | 68.8 ± 9.3 (161) | 0.2573 |
| | [43.0, 91.0] | [47.0, 89.0] | |
| **Gender** | | | |
| Male | 87 / 152 (57.2%) | 93 / 161 (57.8%) | 1.0000 |
| Female | 65 / 152 (42.8%) | 68 / 161 (42.2%) | 1.0000 |
| **Race** | | | |
| African American / Black | 9 / 152 (5.9%) | 12 / 161 (7.5%) | 0.6554 |
| Alaska Native | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| American Indian | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| Asian | 1 / 152 (0.7%) | 2 / 161 (1.2%) | 1.0000 |
| Caucasian / White | 139 / 152 (91.4%) | 146 / 161 (90.7%) | 0.8454 |
| Native Hawaiian / Pacific Islander | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| Unknown | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| Other | 3 / 152 (2.0%) | 1 / 161 (0.6%) | 0.3587 |
| Refuse to disclose | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| **Ethnicity** | | | |
| Hispanic or Latino | 8 / 138 (5.8%) | 8 / 147 (5.4%) | 1.0000 |
| Not Hispanic or Latino | 67 / 138 (48.6%) | 75 / 147 (51.0%) | 0.7227 |
| Unknown | 36 / 138 (26.1%) | 33 / 147 (22.4%) | 0.4919 |
| Refuse to disclose | 27 / 138 (19.6%) | 31 / 147 (21.1%) | 0.7704 |
| | | | |
| **BMI** | 27.5 ± 4.7 (149) | 27.2 ± 4.9 (159) | 0.2020 |
| | [10.5, 49.6] | [16.8, 52.4] | |
| **BMI >=30** | 38 / 149 (25.5%) | 33 / 159 (20.8%) | 0.3455 |
| **History of Smoking** | | | |
| Current | 51 / 152 (33.6%) | 54 / 161 (33.5%) | 1.0000 |
| Past | 72 / 152 (47.4%) | 70 / 161 (43.5%) | 0.4979 |
| Never | 29 / 152 (19.1%) | 37 / 161 (23.0%) | 0.4094 |
| | | | |
| **Hypertension requiring treatment** | 137 / 152 (90.1%) | 139 / 161 (86.3%) | 0.3815 |
| **Hyperlipidemia requiring treatment** | 131 / 152 (86.2%) | 139 / 161 (86.3%) | 1.0000 |
| **Aortic Disease** | 13 / 152 (8.6%) | 12 / 161 (7.5%) | 0.8355 |
| **Carotid Disease** | 37 / 152 (24.3%) | 25 / 161 (15.5%) | 0.0647 |
| **Coronary Artery Disease** | 48 / 152 (31.6%) | 75 / 161 (46.6%) | 0.0077 |
| **Congestive heart failure** | 9 / 152 (5.9%) | 20 / 161 (12.4%) | 0.0527 |
| **NYHA Class** | | | |

| Parameter | Chocolate Touch DCB | Lutonix DCB | P-value[1] |
|---|---|---|---|
| I | 2 / 9 (22.2%) | 4 / 20 (20.0%) | 1.0000 |
| II | 1 / 9 (11.1%) | 4 / 20 (20.0%) | 1.0000 |
| III | 2 / 9 (22.2%) | 2 / 20 (10.0%) | 0.5680 |
| IV | 0 / 9 (0.0%) | 0 / 20 (0.0%) | |
| Missing/Unknown | 4 / 9 (44.4%) | 10 / 20 (50.0%) | 1.0000 |
| **COPD** | 18 / 152 (11.8%) | 23 / 161 (14.3%) | 0.6157 |
| **Coronary Percutaneous Intervention** | 34 / 151 (22.5%) | 48 / 161 (29.8%) | 0.1581 |
| **Coronary Artery Bypass Surgery** | 17 / 152 (11.2%) | 21 / 161 (13.0%) | 0.7296 |
| **Deep vein Thrombosis** | 5 / 152 (3.3%) | 11 / 161 (6.8%) | 0.2013 |
| **Renal Insufficiency History** | 18 / 152 (11.8%) | 13 / 161 (8.1%) | 0.3441 |
| **Cerebrovascular event** | 12 / 152 (7.9%) | 22 / 161 (13.7%) | 0.1063 |
| **Transient Ischemic Attack (TIA)** | 6 / 152 (3.9%) | 11 / 161 (6.8%) | 0.3223 |
| **Cerebrovascular Accident (CVA) or Stroke** | 7 / 152 (4.6%) | 13 / 161 (8.1%) | 0.2516 |
| **Diabetes mellitus** | 66 / 152 (43.4%) | 53 / 161 (32.9%) | 0.0627 |
| **Insulin Dependent** | 21 / 152 (13.8%) | 21 / 161 (13.0%) | 0.8695 |
| **Non-Insulin Dependent** | 45 / 152 (29.6%) | 32 / 161 (19.9%) | 0.0497 |
| **Baseline Rutherford** | | | |
| **Parameter** | **Chocolate Touch DCB** | **Lutonix DCB** | **P-value[1]** |
| 2 | 27 / 152 (17.8%) | 23 / 160 (14.4%) | 0.4431 |
| 3 | 117 / 152 (77.0%) | 128 / 160 (80.0%) | 0.5817 |
| 4 | 8 / 152 (5.3%) | 9 / 160 (5.6%) | 1.0000 |
| **Baseline ABI** | 0.71 ± 0.16 (150) | 0.75 ± 0.22 (154) | 0.1866 |
| | [0.20, 1.17] | [0.21, 1.70] | |
| **Prior interventions with paclitaxel coated devices** | 32 / 141 (22.7%) | 34 / 147 (23.1%) | 1.0000 |

1 Categorical variables compared using Fisher's Exact test. Continuous variables compared using the Wilcoxon Rank Sum Test.

Baseline lesion characteristics were similar between the Chocolate Touch DCB and Lutonix DCB groups. The total lesion length treated was similar between treatment groups (Chocolate Touch 87.1 mm, Lutonix DCB 86.3 mm; p=0.8255). Reference vessel diameter was the same for both groups (5.4 mm; p=0.7294). The baseline lesion characteristics are summarized in **Table 12**. A significant difference was noted in the use of DCB as the final treatment, with the Chocolate Touch being the final treatment 67.8% of the time vs the Lutonix DCB being the final treatment 79.5% of the time (p=0.0208). This difference may be associated with the site reported assessment of residual diameter stenosis (>30%) post DCB, which was present in 17.8% of Chocolate Touch subjects and 10.6% of Lutonix DCB subjects.

**Table 12. Baseline Lesion Characteristics**

| Parameter | Chocolate Touch DCB | Lutonix DCB | P-value[1] |
|---|---|---|---|
| **Lesion Location** | | | |
| **Proximal Segment** | | | |
| Iliac | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| Common Femoral | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| SFA | 137 / 152 (90.1%) | 150 / 161 (93.2%) | 0.4135 |
| Popliteal | 15 / 152 (9.9%) | 10 / 161 (6.2%) | 0.2977 |
| Anterior Tibial | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| Tibial-Peroneal trunk | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |

| | | | |
|---|---|---|---|
| Posterior Tibial | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| Peroneal | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| **Distal Segment** | | | |
| Iliac | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| Common Femoral | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| SFA | 115 / 152 (75.7%) | 132 / 161 (82.0%) | 0.2120 |
| Popliteal | 37 / 152 (24.3%) | 29 / 161 (18.0%) | 0.2120 |
| Anterior Tibial | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| Tibial-Peroneal trunk | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| Posterior Tibial | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| Peroneal | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| | | | |
| **Reference Vessel Diameter (RVD) (visual estimate) – proximal, mm** | 5.4 ± 0.6 (152) | 5.4 ± 0.6 (160) | 0.7294 |
| | [3.6, 6.0] | [4.0, 6.1] | |
| **Reference Vessel Diameter (RVD) (visual estimate) – Distal, mm** | 5.4 ± 0.6 (151) | 5.4 ± 0.6 (160) | 0.9868 |
| | [3.6, 6.0] | [4.0, 6.0] | |
| **Worst % Diameter Stenosis (visual estimate), %** | 90.4 ± 8.6 (152) | 89.4 ± 9.2 (161) | 0.3636 |
| | [70.0, 100.0] | [70.0, 100.0] | |
| **Total Lesion Length, mm** | 87.1 ± 48.3 (152) | 86.3 ± 50.4 (161) | 0.8255 |
| | [5.0, 180.0] | [10.0, 180.0] | |
| **Tandem Lesion** | 5 / 152 (3.3%) | 6 / 161 (3.7%) | 1.0000 |
| **If yes, distance between lesions, mm** | 11.5 ± 6.0 (4) | 17.3 ± 4.6 (3) | 0.1384 |
| | [6.0, 20.0] | [12.0, 20.0] | |
| **Parameter** | **Chocolate Touch DCB** | **Lutonix DCB** | **P-value[1]** |
| **Lesion(s) Type** | | | |
| DeNovo Lesion | 139 / 152 (91.4%) | 150 / 161 (93.2%) | 0.6722 |
| Restenotic Lesion | 13 / 152 (8.6%) | 11 / 161 (6.8%) | 0.6722 |
| **Lesion Calcification** | | | |
| None | 46 / 143 (32.2%) | 44 / 150 (29.3%) | 0.6145 |
| Mild | 49 / 143 (34.3%) | 56 / 150 (37.3%) | 0.6267 |
| Moderate | 48 / 143 (33.6%) | 50 / 150 (33.3%) | 1.0000 |
| Severe | 0 / 143 (0.0%) | 0 / 150 (0.0%) | |
| **DCB TREATMENT** | | | |
| **Diameter Stenosis (after pre-dilatation), %[2]** | 30.2 ± 15.2 (121) | 28.5 ± 17.3 (129) | 0.2019 |
| **Number of DCB used at Target Lesion** | | | |
| 0 | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| 1 | 106 / 152 (69.7%) | 113 / 161 (70.2%) | 1.0000 |
| 2 | 45 / 152 (29.6%) | 45 / 161 (28.0%) | 0.8030 |
| >2 | 1 / 152 (0.7%) | 3 / 161 (1.9%) | 0.6232 |
| **POST DCB ASSESSMENT** | | | |
| **Total DCB Treated Length, mm** | 108.1 ± 46.9 (150) | 112.9 ± 49.9 (159) | 0.4297 |
| | [20.0, 230.0] | [20.0, 240.0] | |
| **DCB(s) covered the pre-treated target lesion length** | 152 / 152 (100.0%) | 159 / 161 (98.8%) | 0.4988 |
| **Residual % Diameter Stenosis[2]** | 16.3 ± 17.8 (152) | 13.8 ± 16.6 (161) | 0.1627 |
| | [0.0, 100.0] | [0.0, 95.0] | |

| | | | |
|---|---|---|---|
| **Final outcome post-DCB treatment** | | | |
| Successful (< 30% DS) | 99 / 152 (65.1%) | 117 / 161 (72.7%) | 0.1786 |
| Dissection | 31 / 152 (20.4%) | 35 / 161 (21.7%) | 0.7834 |
| Residual Diameter Stenosis | 27 / 152 (17.8%) | 17 / 161 (10.6%) | 0.0747 |
| Distal embolization | 1 / 152 (0.7%) | 1 / 161 (0.6%) | 1.0000 |
| Pseudoaneurysm | 0 / 152 (0.0%) | 0 / 161 (0.0%) | |
| Perforation | 0 / 152 (0.0%) | 1 / 161 (0.6%) | 1.0000 |
| Thrombus | 1 / 152 (0.7%) | 2 / 161 (1.2%) | 1.0000 |
| Other | 5 / 152 (3.3%) | 3 / 161 (1.9%) | 0.4912 |
| **Dissection Type** | | | |
| Type A | 9 / 31 (29.0%) | 11 / 35 (31.4%) | 1.0000 |
| Type B | 7 / 31 (22.6%) | 11 / 35 (31.4%) | 0.5807 |
| Type C | 8 / 31 (25.8%) | 5 / 35 (14.3%) | 0.3536 |
| Type D | 6 / 31 (19.4%) | 6 / 35 (17.1%) | 1.0000 |
| Type E | 1 / 31 (3.2%) | 2 / 35 (5.7%) | 1.0000 |
| Type F | 0 / 31 (0.0%) | 0 / 35 (0.0%) | |
| Type Unknown | 0 / 31 (0.0%) | 0 / 35 (0.0%) | |
| **DCB = final treatment** | 103 / 152 (67.8%) | 128 / 161 (79.5%) | 0.0208 |

1 Categorical variables compared using Fisher's Exact test. Continuous variables compared using the Wilcoxon Rank Sum Test.

2 Diameter stenosis was site reported

## D. Safety and Effectiveness Results

### 1. Safety Results

The analysis of safety was based on the ITT cohort of 293 patients/procedures (144 Chocolate Touch DCB and 149 Lutonix DCB) available for 12-month evaluation. The primary safety endpoint was defined as freedom from major adverse events (MAEs) within 12 months of the study procedure. MAEs were defined as a composite of target limb related death, amputation of the target limb, and re-intervention of the target limb. Freedom from MAE at 12 months occurred in 88.9% (128/144) of subjects in the Chocolate Touch group and 84.6% (126/149) of subjects in the Lutonix DCB group (difference, 4.3% [95% CI, -3.4%, 12.1%]) in the primary ITT analysis set as presented in **Table 13**. Therefore, non-inferiority of Chocolate Touch to Lutonix DCB (based on a 10% absolute non-inferiority margin) was met ($P_{non\text{-}inferiority}$=0.0001). The superiority criterion for Chocolate Touch DCB to the Lutonix DCB was not met for the primary safety endpoint ($P_{superiority}$=0.2738).

**Table 13. Primary Safety Endpoint, Freedom from MAE at 12 months as adjudicated by the CEC – ITT**

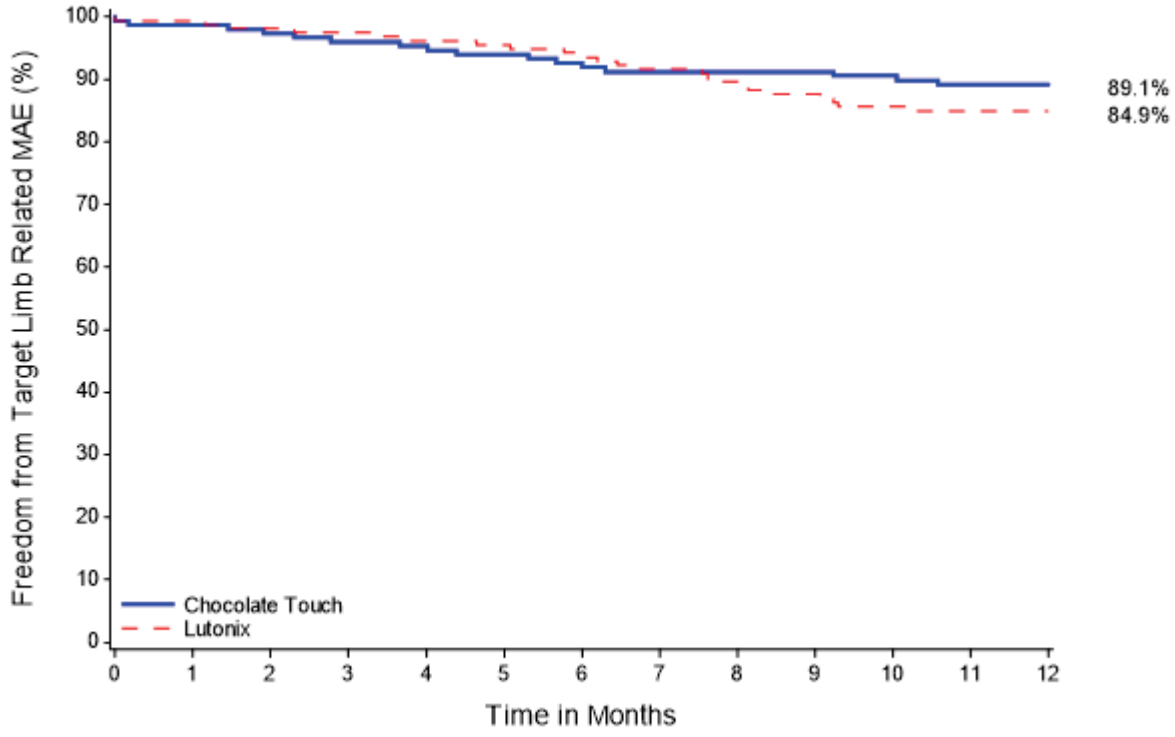
| | #/#(%) (95% CI)[1] | | | | | |
|---|---|---|---|---|---|---|
| **Event** | **Chocolate Touch DCB** | **Lutonix DCB** | **Total** | **Difference (95% CI)[2]** | **Non-Inferiority P- Value[2]** | **Superiority P- Value[2]** |
| **Freedom from MAE** | 128 / 144 (88.9%) (82.6%, 93.5%) | 126 / 149 (84.6%) (77.7%, 90.0%) | 254 / 293 (86.7%) (82.3%, 90.4%) | 4.3% (-3.4%, 12.1%) | 0.0001 | 0.2738 |
| Target Limb Related Death | 1 / 144 (0.7%) (0.0%, 3.8%) | 0 / 149 (0.0%) (0.0%, 2.4%) | 1 / 293 (0.3%) (0.0%, 1.9%) | 0.7% (-0.7%, 2.1%) | | |
| Major Amputation of the Target Limb | 0 / 143 (0.0%) (0.0%, 2.5%) | 0 / 149 (0.0%) (0.0%, 2.4%) | 0 / 292 (0.0%) (0.0%, 1.3%) | - | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Re-Intervention of the Target Limb | 15 / 143 (10.5%) (6.0%, 16.7%) | 23 / 149 (15.4%) (10.0%, 22.3%) | 38 / 292 (13.0%) (9.4%, 17.4%) | -4.9% (-12.6%, 2.7%) | | |

NOTE: Subjects are counted only once within each category.
Denominators include all subjects who have the indicated event or who have adequate follow-up at 12 Months.
[1] Exact 95% confidence intervals.
[2] P-value from the Z-test for the difference in proportion with un-pooled variance. Non-inferiority P- value tested versus the absolute non-inferiority margin of 10%. Confidence interval from the corresponding normal approximation.

The Kaplan-Meier (KM) curve for Freedom from Primary Safety Endpoint through 12 months is presented in **Figure 5**.

**Figure 5. Kaplan-Meier Curve for Freedom from Target Limb Related MAE at 12 months - ITT Analysis Set**

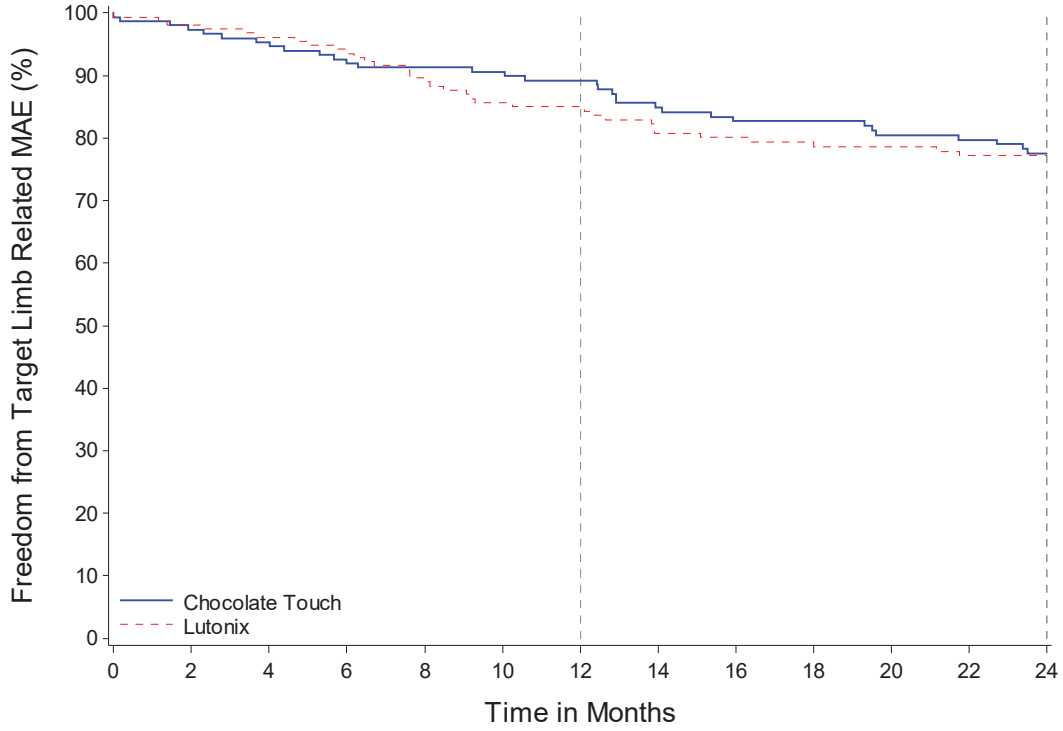



| Months Since Index Procedure | 0 | 1 | 6 | 12 | Logrank P-value[1] |
|---|---|---|---|---|---|
| **Chocolate Touch DCB** | | | | | 0.3174 |
| Survival (95% CI) | 100.0% (100.0%,100.0%) | 98.7% (96.9%,100.0%) | 92.6% (88.4%,96.8%) | 89.1% (84.1%,94.2%) | |
| Number with Event | 0 | 2 | 11 | 16 | |
| Number Remaining at Risk | 152 | 148 | 136 | 97 | |
| **Lutonix DCB** | | | | | |
| Survival (95% CI) | 100.0% (100.0%,100.0%) | 99.4% (98.2%,100.0%) | 94.2% (90.5%,97.9%) | 84.9% (79.2%,90.6%) | |
| Number with Event | 0 | 1 | 9 | 23 | |
| Number Remaining at Risk | 161 | 155 | 145 | 108 | |

[1]The p-value should be interpreted with caution because a hypothesis test for the survival endpoint was not pre-specified and was not adjusted for multiplicity.

The Kaplan-Meier (KM) curve for Freedom from target limb related MAE at 24 months is presented in **Figure 6.**

**Figure 6. Kaplan-Meier Curve for Freedom from Target Limb Related MAE at 24mo* - ITT Analysis Set**




*NOTE: 24month data provided in this graph is an interim analysis and should be interpreted with caution. Data at 24 months is not complete and is not fully adjudicated at this time.

| Months Since Index Procedure | 0 | 1 | 6 | 12 | 24 |
|---|---|---|---|---|---|
| **Chocolate Touch** | | | | | |
| Survival (95% CI) | 100.0% (100.0%,100.0%) | 98.7% (96.9%,100.0%) | 92.6% (88.4%,96.8%) | 89.2% (84.2%,94.2%) | 77.5% (70.6%,84.4%) |
| Number with Event | 0 | 2 | 11 | 16 | 32 |
| Number Remaining at Risk | 152 | 148 | 137 | 127 | 92 |
| **Lutonix** | | | | | |
| Survival (95% CI) | 100.0% (100.0%,100.0%) | 99.4% (98.2%,100.0%) | 94.2% (90.5%,97.9%) | 85.0% (79.4%,90.7%) | 77.2% (70.4%,83.9%) |
| Number with Event | 0 | 1 | 9 | 23 | 34 |
| Number Remaining at Risk | 161 | 155 | 145 | 124 | 95 |

## Adverse events that occurred in the PMA clinical study

Site-reported serious adverse events (SAEs) through 12 months are shown in **Table 14**. A SAE was defined as an event, which leads to death due to any cause, life-threatening condition, persistent or significant disability/incapacity, requires in-patient hospitalization or prolonged hospitalization, intervention to prevent

permanent impairment of body function or permanent damage to body structure, and congenital abnormality. As presented below, the rate of serious adverse event was low and comparable between groups. No unanticipated adverse device effects occurred.

**Table 14. Treatment Emergent Serious Adverse Events Through 12 Months – ITT Analysis Set**

| | Chocolate Touch DCB | | Lutonix DCB | | Total | |
|---|---|---|---|---|---|---|
| **Adverse Event Code** | **#** | **#(%) Patients** | **#** | **#(%) Patients** | **#** | **#(%) Patients** |
| **Total** | 111 | 73 / 152 (48.0%) | 141 | 73 / 161 (45.3%) | 252 | 146 / 313 (46.6%) |
| **Angiographic / Procedural Events (A)** | 4 | 4 / 152 (2.6%) | 6 | 6 / 161 (3.7%) | 10 | 10 / 313 (3.2%) |
| A1: Access site complication requiring surgery or transfusion | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| A2: Arterial occlusion or thrombus at puncture site | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| A3: Arterial perforation or rupture (vessel) | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| A6: Embolization, distal | 3 | 3 / 152 (2.0%) | 0 | 0 / 161 (0.0%) | 3 | 3 / 313 (1.0%) |
| A7: Groin hematoma _5cm, with or without surgical repair | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| A8: Hematoma at access site | 1 | 1 / 152 (0.7%) | 1 | 1 / 161 (0.6%) | 2 | 2 / 313 (0.6%) |
| A9: Perforation / Extravasation of contrast media | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| A10: Thrombosis | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| A11: Thromboembolic episodes | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| A12: Vessel spasm or recoil | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| | | | | | | |
| **Cardiac I** | 23 | 19 / 152 (12.5%) | 12 | 10 / 161 (6.2%) | 35 | 29 / 313 (9.3%) |
| C1: Angina | 6 | 4 / 152 (2.6%) | 1 | 1 / 161 (0.6%) | 7 | 5 / 313 (1.6%) |
| C2: Atrial Fibrillation | 3 | 3 / 152 (2.0%) | 4 | 2 / 161 (1.2%) | 7 | 5 / 313 (1.6%) |
| C3: Cardiac arrest | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| C4: Cardiac arrhythmia | 1 | 1 / 152 (0.7%) | 2 | 2 / 161 (1.2%) | 3 | 3 / 313 (1.0%) |
| C5: Cardiogenic shock | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| C6: Congestive Heart Failure | 1 | 1 / 152 (0.7%) | 1 | 1 / 161 (0.6%) | 2 | 2 / 313 (0.6%) |
| C7: Coronary artery disease | 7 | 7 / 152 (4.6%) | 2 | 2 / 161 (1.2%) | 9 | 9 / 313 (2.9%) |
| C8: Hypertension | 1 | 1 / 152 (0.7%) | 0 | 0 / 161 (0.0%) | 1 | 1 / 313 (0.3%) |
| C9: Hypotension | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| C10: Myocardial infarction | 3 | 3 / 152 (2.0%) | 1 | 1 / 161 (0.6%) | 4 | 4 / 313 (1.3%) |
| C11: Myocardial ischemia | 1 | 1 / 152 (0.7%) | 0 | 0 / 161 (0.0%) | 1 | 1 / 313 (0.3%) |
| C12 Ventricular fibrillation | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| C13: Ventricular tachycardia | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| | | | | | | |
| **Hematological (H)** | 4 | 4 / 152 (2.6%) | 2 | 2 / 161 (1.2%) | 6 | 6 / 313 (1.9%) |
| H1: Anemia | 1 | 1 / 152 (0.7%) | 1 | 1 / 161 (0.6%) | 2 | 2 / 313 (0.6%) |
| H2: Bacteremia | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| H3: Bleeding, from anticoagulant or antiplatelet meds | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| H4: Disseminated intravascular coagulation | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| H5: Hemorrhage, with or without transfusion | 1 | 1 / 152 (0.7%) | 0 | 0 / 161 (0.0%) | 1 | 1 / 313 (0.3%) |

| | Chocolate Touch DCB | | Lutonix DCB | | Total | |
|---|---|---|---|---|---|---|
| **Adverse Event Code** | **#** | **#(%) Patients** | **#** | **#(%) Patients** | **#** | **#(%) Patients** |
| H6: Septicemia or sepsis | 2 | 2 / 152 (1.3%) | 0 | 0 / 161 (0.0%) | 2 | 2 / 313 (0.6%) |
| | | | | | | |
| **Neurological (N)** | 1 | 1 / 152 (0.7%) | 1 | 1 / 161 (0.6%) | 2 | 2 / 313 (0.6%) |
| N1: Cerebrovascular Accident (CVA, stroke) | 1 | 1 / 152 (0.7%) | 0 | 0 / 161 (0.0%) | 1 | 1 / 313 (0.3%) |
| N2: Seizure | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| N3: Transient Ischemic Attack (TIA) | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| | | | | | | |
| **Pulmonary (P)** | 2 | 2 / 152 (1.3%) | 3 | 2 / 161 (1.2%) | 5 | 4 / 313 (1.3%) |
| P1: Chronic Obstructive Pulmonary Disease (COPD) | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| P2: Pneumonia | 2 | 2 / 152 (1.3%) | 2 | 1 / 161 (0.6%) | 4 | 3 / 313 (1.0%) |
| P3: Pulmonary edema | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| P4: Pulmonary embolism | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| P5: Respiratory arrest | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| P6: Respirator distress | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| P7: Respiratory failure | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| | | | | | | |
| **Renal I** | 1 | 1 / 152 (0.7%) | 2 | 2 / 161 (1.2%) | 3 | 3 / 313 (1.0%) |
| R1: Renal failure | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| R2: Renal insufficiency | 1 | 1 / 152 (0.7%) | 2 | 2 / 161 (1.2%) | 3 | 3 / 313 (1.0%) |
| | | | | | | |
| **Vascular / Peripheral Vascular (V)** | 35 | 28 / 152 (18.4%) | 82 | 45 / 161 (28.0%) | 117 | 73 / 313 (23.3%) |
| V1: Abrupt occlusion | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| V2: Amputation, major (above or at the ankle) | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| V3: Amputation, minor (below the ankle) | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| V4: Aneurysm | 0 | 0 / 152 (0.0%) | 3 | 3 / 161 (1.9%) | 3 | 3 / 313 (1.0%) |
| V5: Arterial stenosis (non-target – lesion or vessel; not restenosis) | 7 | 7 / 152 (4.6%) | 18 | 13 / 161 (8.1%) | 25 | 20 / 313 (6.4%) |
| V6: Arteriovenous fistula | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| V7: Claudication, recurrent or worsening | 1 | 1 / 152 (0.7%) | 7 | 7 / 161 (4.3%) | 8 | 8 / 313 (2.6%) |
| V8: Ischemic ulcer | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| V9: Necrosis | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| V10: Peripheral ischemia (lower extremity) | 0 | 0 / 152 (0.0%) | 2 | 2 / 161 (1.2%) | 2 | 2 / 313 (0.6%) |
| V11: Pseudoaneurysm | 2 | 2 / 152 (1.3%) | 1 | 1 / 161 (0.6%) | 3 | 3 / 313 (1.0%) |
| V12: Restenosis of the non-target vessel (target or non-target limb) | 9 | 7 / 152 (4.6%) | 15 | 9 / 161 (5.6%) | 24 | 16 / 313 (5.1%) |
| V13: Restenosis of the target lesion (treated segment) | 10 | 9 / 152 (5.9%) | 20 | 19 / 161 (11.8%) | 30 | 28 / 313 (8.9%) |
| V14: Restenosis of the target vessel (treated vessel) | 4 | 4 / 152 (2.6%) | 10 | 9 / 161 (5.6%) | 14 | 13 / 313 (4.2%) |
| V15: Thrombophlebitis | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| V16: Total occlusion of a peripheral artery | 2 | 2 / 152 (1.3%) | 4 | 4 / 161 (2.5%) | 6 | 6 / 313 (1.9%) |
| | | | | | | |
| **Other (O)** | 41 | 35 / 152 (23.0%) | 33 | 25 / 161 (15.5%) | 74 | 60 / 313 (19.2%) |

| | Chocolate Touch DCB | | Lutonix DCB | | Total | |
|---|---|---|---|---|---|---|
| **Adverse Event Code** | **#** | **#(%) Patients** | **#** | **#(%) Patients** | **#** | **#(%) Patients** |
| O1: Allergic reaction (medication, contrast media, device, etc.) | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| O2: Fever (>38.3oC / 101oF) | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| O3: Gastrointestinal bleeding | 0 | 0 / 152 (0.0%) | 1 | 1 / 161 (0.6%) | 1 | 1 / 313 (0.3%) |
| O4: Headache related to anesthesia (>24 hrs after procedure) | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |
| O5: Infected peripheral wound | 2 | 1 / 152 (0.7%) | 1 | 1 / 161 (0.6%) | 3 | 2 / 313 (0.6%) |
| O6: Infection | 1 | 1 / 152 (0.7%) | 1 | 1 / 161 (0.6%) | 2 | 2 / 313 (0.6%) |
| O7: Pain | 2 | 2 / 152 (1.3%) | 1 | 1 / 161 (0.6%) | 3 | 3 / 313 (1.0%) |
| O8: Urinary tract infection (UTI) | 1 | 1 / 152 (0.7%) | 1 | 1 / 161 (0.6%) | 2 | 2 / 313 (0.6%) |
| O9: Other | 35 | 31 / 152 (20.4%) | 26 | 19 / 161 (11.8%) | 61 | 50 / 313 (16.0%) |
| Other NOT SPECIFIED | 0 | 0 / 152 (0.0%) | 0 | 0 / 161 (0.0%) | 0 | 0 / 313 (0.0%) |

2. *Effectiveness Results*

The analysis of effectiveness was based on the 267 (137 Chocolate Touch and 130 Lutonix DCB) evaluable patients at the 12-month time point. The primary effectiveness endpoint of the Chocolate Touch study was True DCB Success at 12 months, defined as primary patency in the absence of clinically driven bail-out stenting. Specifically, primary patency was defined as the absence of target lesion restenosis (as assessed by duplex ultrasound review based on Peak Systolic Velocity Ratio (PSVR) <2.4) and freedom from clinically driven target lesion revascularization (CD-TLR) through 12 months. In the primary ITT analysis set, 85.3% of all subjects had sufficient data to assess True DCB Success at 12 months (missing data included 9.9% Chocolate Touch subjects vs 19.3% for Lutonix DCB subjects). This rate is consistent with the assumed 15% loss to follow-up for the primary effectiveness endpoint that was assumed when determining the required sample size. Key effectiveness outcomes are presented in **Table 15**. The Kaplan Meier Curve for True DCB Success through 12 months is presented in **Figure 7**. As shown in the data below, the Chocolate Touch met its primary endpoint of non-inferiority compared to the Lutonix DCB. Given that non-inferiority of the effectiveness endpoint was met, a pre-specified superiority analysis for effectiveness of Chocolate Touch to Lutonix DCB was conducted and met (Psuperiority=0.0386). However, the imbalance in missing data between treatment groups adds uncertainty to the superiority results. The results of a tipping point analysis demonstrate that the superiority result is not robust. Further, the statistically significant difference in True DCB success between the groups at 12 months was not maintained at 24 months.

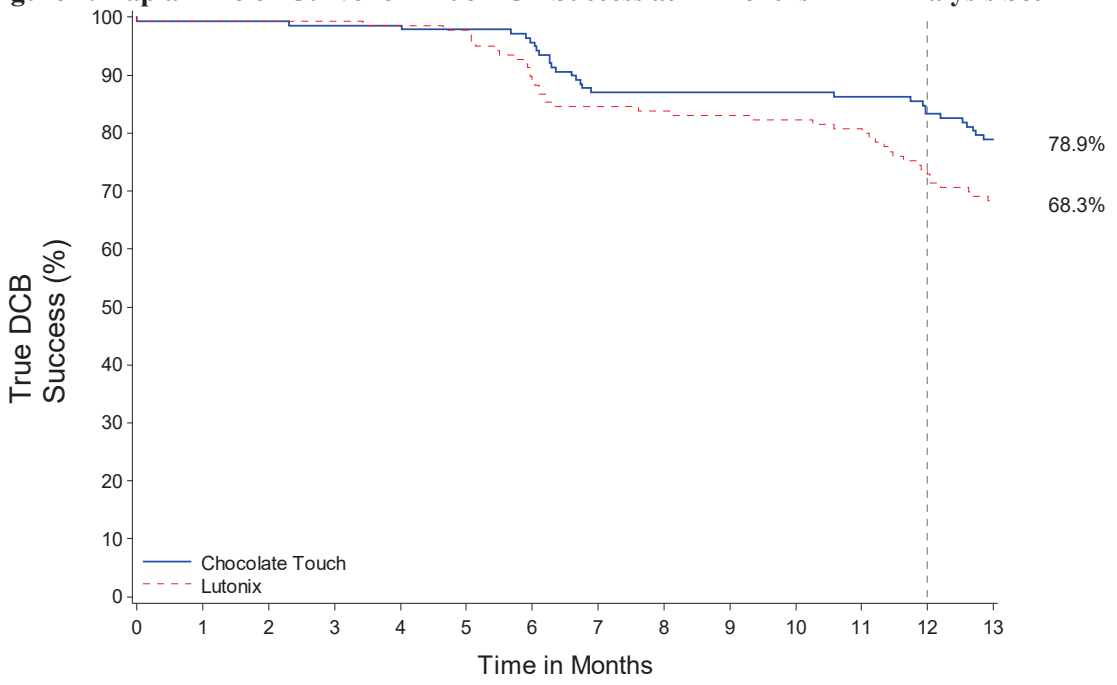
**Table 15. Primary Effectiveness Endpoint, True DCB Success at 12 Months – ITT**

| | #/#(%) (95% CI)[1] | | | | | |
|---|---|---|---|---|---|---|
| **Event** | **Chocolate Touch DCB** | **Lutonix DCB** | **Total** | **Difference (95% CI)[2]** | **Non-Inferiority P-Value[2]** | **Superiority P-Value[2]** |
| **True DCB Success** | 108 / 137 (78.8%) (71.0%, 85.3%) | 88 / 130 (67.7%) (58.9%, 75.6%) | 196 / 267(73.4%) (67.7%, 78.6%) | 11.1% (0.6%,21.7%) | <.0001 | 0.0386 |
| CD-stent | 0 / 152 (0.0%) (0.0%, 2.4%) | 0 / 161 (0.0%) (0.0%, 2.3%) | 0 / 313 (0.0%) (0.0%, 1.2%) | - | | |

| Event | #/#(%) (95% CI)[1] | | | | | |
|---|---|---|---|---|---|---|
| | Chocolate Touch DCB | Lutonix DCB | Total | Difference (95% CI)[2] | Non-Inferiority P-Value[2] | Superiority P-Value[2] |
| Primary Patency | 108 / 137 (78.8%) (71.0%, 85.4%) | 88 / 130 (67.7%) (58.9%, 75.6%) | 196 / 267(73.4%) (67.7%, 78.6%) | 11.1% (0.6%,21.7%) | | |

NOTE: Success is defined as completion of the 12 month visit at day 334 or greater with a patent DUS finding and no occurrence of a clinically driven target lesion revascularization prior to the 12 month visit and no placement of CD-stent during the index procedure. A patent DUS finding at a subsequent visit can be imputed for a missing DUS at the 12 month visit given no intervening target lesion revascularization.
1 Exact 95% confidence intervals.
2 P-value from the Z-test for the difference in proportion with un-pooled variance. Non-inferiority P-value tested versus the absolute non-inferiority margin of 10%. Confidence interval from the corresponding normal approximation.

**Figure 7. Kaplan-Meier Curve for True DCB Success at 12 months - ITT Analysis Set**

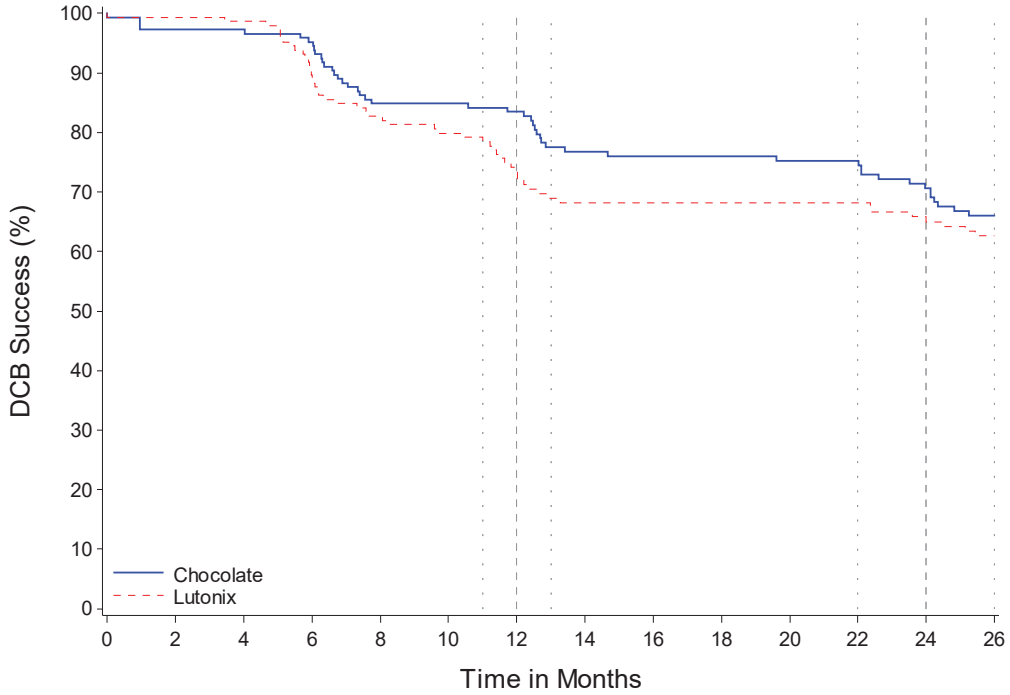



| Months Since Index Procedure | 0 | 1 | 6 | 12 | 13 | Logrank P-value[1] |
|---|---|---|---|---|---|---|
| **Chocolate Touch** | | | | | | 0.0429 |
| Survival (95% CI) | 100.0% (100.0%,100.0%) | 99.3% (97.9%,100.0%) | 96.4% (93.3%,99.5%) | 83.3% (77.1%,89.5%) | 78.9% (72.1%,85.7%) | |
| Number with Event | 0 | 1 | 5 | 23 | 29 | |
| Number Remaining at Risk | 140 | 139 | 134 | 113 | 107 | |
| **Lutonix** | | | | | | |
| Survival (95% CI) | 100.0% (100.0%,100.0%) | 99.3% (97.9%,100.0%) | 91.3% (86.6%,96.0%) | 73.0% (65.4%,80.5%) | 68.3% (60.3%,76.2%) | |
| Number with Event | 0 | 1 | 12 | 36 | 42 | |
| Number Remaining at Risk | 139 | 138 | 123 | 94 | 88 | |

NOTE: Subjects with an assessment of patent within the 12- month analysis window, are censored at the end of the window (month 13), otherwise subjects are censored at their last known patency assessment. Days to loss of patency are calculated as the time to earliest loss of patency for subjects not patent at 12 months via DUS, or as the time to CDTLR, whichever comes first.
[1]The p-value should be interpreted with caution because a hypothesis test for the survival endpoint was not pre-specified and was not adjusted for multiplicity.

The Kaplan-Meier (KM) curve for True DCB Success at 24 months is presented in **Figure 8.**

**Figure 8. Kaplan-Meier Curve for True DCB Success at 24months *- ITT Analysis Set**




*NOTE: 24 month data provided in this graph is an interim analysis and should be interpreted with caution. Data at 24 months is not complete and is not fully adjudicated at this time.

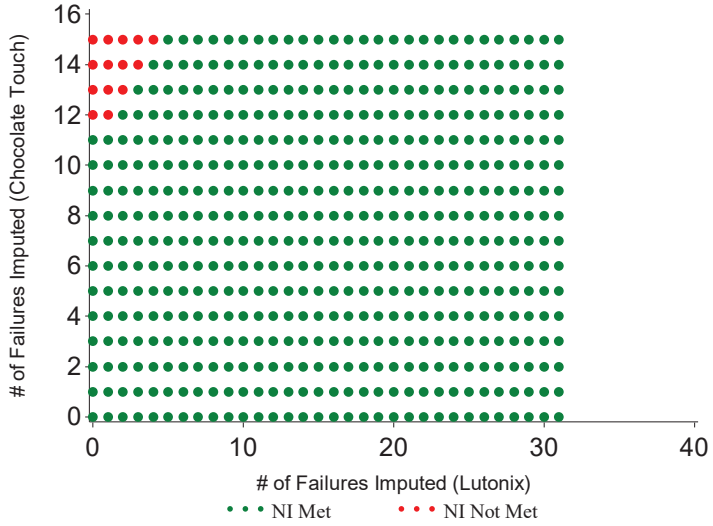
| Months Since Index Procedure | 0 | 1 | 6 | 12 | 13 | 24 | 26 |
|---|---|---|---|---|---|---|---|
| **Chocolate Touch** | | | | | | | |
| Survival (95% CI) | 100.0% (100.0%,100.0%) | 97.3% (94.7%,99.9%) | 95.2% (91.8%,98.7%) | 83.4% (77.4%,89.5%) | 77.5% (70.6%,84.4%) | 70.6% (63.0%,78.2%) | 66.0% (58.0%,73.9%) |
| Number with Event | 0 | 4 | 7 | 24 | 32 | 41 | 47 |
| Number Remaining at Risk | 149 | 143 | 138 | 115 | 102 | 92 | 75 |
| **Lutonix** | | | | | | | |
| Survival (95% CI) | 100.0% (100.0%,100.0%) | 99.3% (98.0%,100.0%) | 91.1% (86.5%,95.7%) | 73.5% (66.2%,80.7%) | 69.0% (61.4%,76.6%) | 65.0% (57.1%,73.0%) | 62.6% (54.5%,70.7%) |
| Number with Event | 0 | 1 | 13 | 38 | 44 | 49 | 52 |
| Number Remaining at Risk | 151 | 148 | 132 | 100 | 89 | 81 | 71 |

NOTE: Subjects with an assessment of patent within the analysis window, are censored at the end of the window, otherwise subjects are censored at their last known patency assessment. Days to loss of patency are calculated as the time to earliest loss of patency for subjects not patent via DUS, or as the time to CDTLR, whichever comes first.
Dotted lines represent visit windows.

The impact of missing data is evaluated in the sensitivity analyses presented in **Figure 9** for non-inferiority and **Figure 10** for superiority. Tipping point analyses were conducted for the primary effectiveness endpoint in the ITT analysis set to determine at what point of imputation of missing data the significance is lost. The tipping point analysis for the non-inferiority test demonstrated that it is unlikely that missing data would change the non-inferiority result for the primary effectiveness endpoint. As seen in **Figure 9**, at least 80% of subjects with missing data in the Chocolate Touch group would have to be imputed as failures and 100% of subjects with missing data in the Lutonix DCB group imputed as successes. The tipping point analysis for the superiority test raise questions of uncertainty regarding the superiority results. For instance, if all missing outcomes from both groups are imputed as successes, superiority would not be met. Overall, of the 512 possible

combinations of imputations in **Figure 10**, 302 (59%) of imputation scenarios result in superiority continuing to be met, though 41% result in superiority not being met. Thus, the superiority conclusion is not robust.

**Figure 9. True DCB Success at 12 Months, Tipping Point Analysis for Non-Inferiority – ITT Analysis Set**



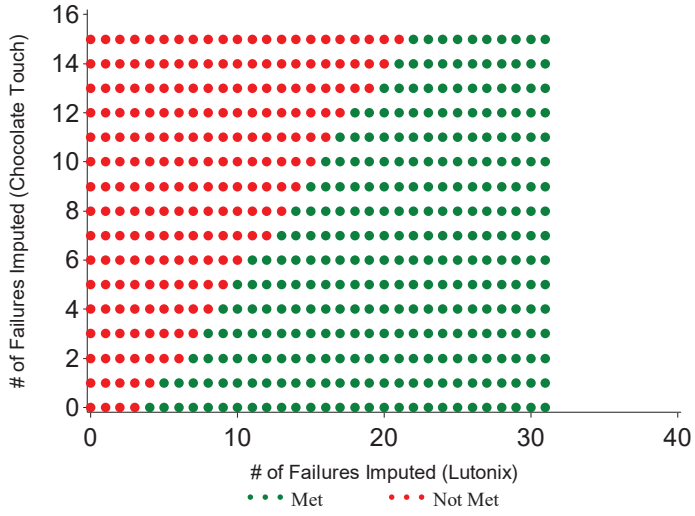

| | Chocolate Touch | | | Lutonix | | | |
|---|---|---|---|---|---|---|---|
| **Variable Description** | **# Missing** | **# Failures Imputed** | **# Successes Imputed** | **# Missing** | **# Failures Imputed** | **# Successes Imputed** | **Non-inferiority Met** |
| Best Case[2] | 15 | 0 | 15 | 31 | 31 | 0 | Yes |
| TIPPING POINT[1] | 15 | 12 | 3 | 31 | 0 | 31 | No |
| Worst Case[3] | 15 | 15 | 0 | 31 | 0 | 31 | No |

[1] Tipping point analysis conducts all possible combinations of imputation between best and worst case to determine at what point of imputation significance is lost. Green dots denote values where the endpoint is met while red dots indicated points where the endpoint the statistical is not met.

[2] Best case analysis imputes success for all Chocolate Touch subjects with missing data and all Lutonix subjects as failures and is the upper bound of the tipping point.

[3] Worst case analysis imputes failures for all Chocolate Touch subjects with missing data and successes for all Lutoni x subjects with missing data and is the lower bound of tipping point.

**Figure 10. True DCB Success at 12 Months, Tipping Point Analysis for Superiority – ITT Analysis Set**



| Variable Description | # Missing | # Failures Imputed | # Successes Imputed | # Missing | # Failures Imputed | # Successes Imputed | Superiority Met |
|---|---|---|---|---|---|---|---|
| Best Case[2] | 15 | 0 | 15 | 31 | 31 | 0 | Yes |
| TIPPING POINT[1] | 15 | 0 | 15 | 31 | 0 | 31 | No |
| Worst Case[3] | 15 | 15 | 0 | 31 | 0 | 31 | No |

[1] Tipping point analysis conducts all possible combinations of imputation between best and worst case to determine at what point of imputation significance is lost. Green dots denote values where the endpoint is met while red dots indicated points where the endpoint the statistical is not met.
[2] Best case analysis imputes success for all Chocolate Heart subjects with missing data and all Lutonix subjects as failures and is the upper bound of the tipping point.
[3] Worst case analysis imputes failures for all Chocolate Heart subjects with missing data and successes for all Lutonix subjects with missing data and is the lower bound of tipping point.

*Secondary Endpoint Results*

A summary of Angiographic Core Lab (ACL)-reported acute secondary endpoints in the primary ITT analysis is presented in **Table 16**. There were no significant differences between treatment groups. Technical and device success in the Chocolate Touch group were 98.0% and 86.0%, respectively, and in the Lutonix DCB group were 99.4% and 85.3%. There were no CD-stents implanted in either treatment group. The rates of any stent placement were similar between treatment groups (7.9% Chocolate Touch vs. 9.4% Lutonix DCB) and the length of stented segment showed numerical differences but were not statistically different (54.3 ± 19.0 mm Chocolate Touch vs. 85.7 ± 53.3 mm Lutonix DCB).

**Table 16. Acute Secondary Endpoints by Angiographic Core Lab Review - ITT Analysis Set**

| | #/#(%) (95% CI) or mean ± SD (n) [min,max] (95% CI) | | | |
|---|---|---|---|---|
| **Parameter** | **Chocolate Touch** | **Lutonix DCB** | **Total** | **Difference[1]** |
| **Technical Success** | 149 / 152 (98.0%) (94.3%, 99.6%) | 160 / 161 (99.4%) (96.6%, 100.0%) | 309 / 313 (98.7%) (96.8%, 99.7%) | -1.4% (-3.9%,1.2%) |
| **Device Success** | 129 / 150 (86.0%) (79.4%, 91.1%) | 133 / 156 (85.3%) (78.7%, 90.4%) | 262 / 306 (85.6%) (81.2%, 89.4%) | 0.7% (-7.1%,8.6%) |
| **CD-Stent[2]** | 0 / 152 (0.0%) (0.0%, 2.4%) | 0 / 161 (0.0%) (0.0%, 2.3%) | 0 / 313 (0.0%) (0.0%, 1.2%) | - |
| **Any Stent Placement** | 12 / 152 (7.9%) (4.1%, 13.4%) | 15 / 160 (9.4%) (5.3%, 15.0%) | 27 / 312 (8.7%) (5.8%, 12.3%) | -1.5% (-7.7%,4.7%) |
| **Length of Stented Segment** | 54.3 ± 19.0 (12) [17.9, 91.3] (42.2,66.3) | 85.7 ± 53.3 (15) [30.5, 217.0] (56.1,115.2) | 71.7 ± 44.0 (27) [17.9, 217.0] (54.3,89.1) | |
| **Ratio of Stented Segment to Lesion Length** | 0.99 ± 0.63 (12) [0.35, 2.29] (0.59,1.39) | 0.98 ± 0.49 (15) [0.21, 1.97] (0.71,1.26) | 0.99 ± 0.55 (27) [0.21, 2.29] (0.77,1.20) | |
| **Any Target Lesion Dissection** | 84 / 152 (55.3%) (47.0%, 63.3%) | 76 / 159 (47.8%) (39.8%, 55.9%) | 160 / 311 (51.4%) (45.7%, 57.1%) | 7.5% (-3.6%,18.5%) |
| **Dissection Type E or F** | 0 / 152 (0.0%) (0.0%, 2.4%) | 0 / 159 (0.0%) (0.0%, 2.3%) | 0 / 311 (0.0%) (0.0%, 1.2%) | - |

| | | | | |
|---|---|---|---|---|
| **Geographic Miss** | 11 / 126 (8.7%) (4.4%, 15.1%) | 7 / 131 (5.3%) (2.2%, 10.7%) | 18 / 257 (7.0%) (4.2%, 10.8%) | 3.4% (-2.9%,9.6%) |

[1] Not adjusted for multiplicity

[2] Adjudicated by the Clinical Events Committee

A summary of DUS-reported secondary endpoints in the primary ITT analysis set at 6- and 12-month follow-up is presented in **Table 17**. True DCB Success at 6 months was similar between treatment groups (85.5% Chocolate Touch vs. 79.9% Lutonix DCB). At 6 and 12 months, there were no significant differences between treatment groups with respect to primary patency, stent-free patency, and secondary patency. Secondary patency rates at 12-month follow-up were similar between groups (83.3% Chocolate Touch vs. 75.6% Lutonix DCB).

**Table 17. Secondary Endpoints, by DUS Core Lab Review – ITT Analysis Set**

| | #/#(%) (95% CI) | | | |
|---|---|---|---|---|
| **Parameter** | **Chocolate Touch** | **Lutonix DCB** | **Total** | **Difference[1]** |
| **True DCB success** | | | | |
| 6 Months | 112 / 131 (85.5%) (78.3%, 91.0%) | 107 / 134 (79.9%) (72.1%, 86.3%) | 219 / 265 (82.6%) (77.5%, 87.0%) | 5.6% (-3.4%,14.7%) |
| 12 Months* | 108/137 (78.8%) (71.0%, 85.3%) | 88/130 (67.7%) (58.9%, 75.6%) | 196/267 (73.4%) (67.7%, 78.6%) | 11.1% (0.6%, 21.7%) |
| **Primary Patency** | | | | |
| 6 Months | 112 / 131 (85.5%) (78.3%, 91.0%) | 107 / 134 (79.9%) (72.1%, 86.3%) | 219 / 265 (82.6%) (77.5%, 87.0%) | 5.6% (-3.4%,14.7%) |
| 12 Months | 108/137 (78.8%) (71.0%, 85.3%) | 88/130 (67.7%) (58.9%, 75.6%) | 196/267 (73.4%) (67.7%, 78.6%) | 11.1% (0.6%, 21.7%) |
| **Stent Free Patency** | | | | |
| 6 Months | 103 / 121 (85.1%) (77.5%, 90.9%) | 95 / 120 (79.2%) (70.8%, 86.0%) | 198 / 241 (82.2%) (76.7%, 86.8%) | 6.0% (-3.7%,15.6%) |
| 12 Months | 98 / 129 (76.0%) (67.7%, 83.1%) | 79 / 120 (65.8%) (56.6%, 74.2%) | 177 / 249 (71.1%) (65.0%, 76.6%) | 10.1% (-1.1%,21.4%) |
| **Secondary Patency** | | | | |
| 6 Months | 114 / 129 (88.4%) (81.5%, 93.3%) | 110 / 134 (82.1%) (74.5%, 88.2%) | 224 / 263 (85.2%) (80.3%, 89.2%) | 6.3% (-2.2%,14.8%) |
| 12 Months | 115 / 138 (83.3%) (76.0%, 89.1%) | 99 / 131 (75.6%) (67.3%, 82.7%) | 214 / 269 (79.6%) (74.2%, 84.2%) | 7.8% (-1.9%,17.4%) |

*This is the primary effectiveness endpoint.

[1] Not adjusted for multiplicity

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: gender, geography (OUS/US), diabetes, baseline Rutherford category, pre-dilatation method, calcification, lesion length, treatment location, and vascular location. Subgroup analyses in the primary ITT analysis set for the primary safety endpoint are

presented in **Table 18** and for the primary efficacy endpoint **Table 19**.

For the safety endpoint, there were no significant treatment interactions (evaluated at a p value of 0.15) in pre-specified subgroup analyses: male vs female (P=0.1545); US vs OUS (P=0.3544); diabetes vs. no diabetes (P=0.9634); baseline Rutherford Classification, ≤3 vs. >3 (P=0.4923); predilatation method, atherectomy vs. standard balloon angioplasty (P=0.8195); calcification, minimal/none vs. moderate/severe (P=0.1546); treatment location, hospital vs. outpatient (P=0.9648); or target lesion location, SFA vs. popliteal (P=0.9736). A significant treatment interaction was observed in a subgroup analysis according to lesion length, ≤10 cm vs. >10 cm (P=0.0484). The rates of freedom from MAE were higher for lesion length ≤10 cm with Chocolate Touch compared with Lutonix DCB: 90.0% vs.73.1%, P=0.0408. These results demonstrate that the relative safety profile of Chocolate Touch was consistent across pre-specified subgroups, with a potential safety benefit in subjects with lesion length ≤10 cm.

**Table 18. Additional Subgroup Analyses: Primary Safety Endpoint of Freedom from MAE at 12 Months**

| | #/#(%) | | | | |
|---|---|---|---|---|---|
| **Subgroup** | **Chocolate Touch** | **Lutonix DCB** | **Difference (95% CI)** | **P-Value[1]** | **Interaction P-Value[2]** |
| **Gender** | | | | | 0.1545 |
| Male | 75 / 84 (89.3%) | 78 / 86 (90.7%) | -1.4% (-10.4%,7.6%) | 0.8029 | |
| Female | 53 / 60 (88.3%) | 48 / 63 (76.2%) | 12.1% (-1.1%,25.4%) | 0.1007 | |
| **Geography** | | | | | 0.3544 |
| US | 43 / 48 (89.6%) | 43 / 54 (79.6%) | 10.0% (-3.8%,23.7%) | 0.1861 | |
| OUS | 85 / 96 (88.5%) | 83 / 95 (87.4%) | 1.2% (-8.1%, 10.4%) | 0.8277 | |
| **Diabetes** | | | | | 0.3544 |
| Diabetes | 55 / 62 (88.7%) | 42 / 50 (84.0%) | 4.7% (-8.1%, 17.6%) | 0.5795 | |
| No Diabetes | 73 / 82 (89.0%) | 84 / 99 (84.8%) | 4.2% (-5.6%, 14.0%) | 0.5107 | |
| **Baseline Rutherford** | | | | | 0.9634 |
| <=3 | 122 / 136 (89.7%) | 121 / 140 (86.4%) | 3.3% (-4.4%, 10.9%) | 0.4602 | |
| >3 | 6 / 8 (75.0%) | 4 / 8 (50.0%) | 25.0% (-20.8%, 70.8%) | 0.6084 | |
| **Predilatation** | | | | | 0.4923 |
| Atherectomy | 16 / 19 (84.2%) | 12 / 16 (75.0%) | 9.2% (-17.6%, 36.0%) | 0.6772 | |
| Standard balloon angioplasty | 112 / 125 (89.6%) | 114 / 133 (85.7%) | 3.9% (-4.1%, 11.9%) | 0.4502 | |
| **Calcification** | | | | | 0.8195 |
| Minimal/None | 81 / 89 (91.0%) | 73 / 92 (79.3%) | 11.7% (1.5%, 21.8%) | 0.0363 | |
| Moderate/Severe | 42 / 47 (89.4%) | 42 / 46 (91.3%) | -1.9% (-13.9%, 10.1%) | 1.0000 | |
| **Lesion Length** | | | | | 0.1546 |
| <=10 cm | 45 / 50 (90.0%) | 38 / 52 (73.1%) | 16.9% (2.3%, 31.6%) | 0.0408 | |
| >10 cm | 83 / 94 (88.3%) | 88 / 97 (90.7%) | -2.4% (-11.1%, 6.3%) | 0.6415 | |
| **Treatment Location** | | | | | 0.0484 |
| *Hospital Based Procedure* | 124 / 138 (89.9%) | 120 / 139 (86.3%) | 3.5% (-4.1%, 11.1%) | 0.4587 | |
| *Outpatient Based Lab* | 4 / 6 (66.7%) | 6 / 10 (60.0%) | 6.7% (-41.8%, 55.1%) | 1.0000 | |
| **Location** | | | | | 0.9648 |
| SFA | 115 / 129 (89.1%) | 117 / 140 (83.6%) | 5.6% (-2.6%, 13.7%) | 0.2165 | |

| | #/#(%) | | | | |
|---|---|---|---|---|---|
| **Subgroup** | **Chocolate Touch** | **Lutonix DCB** | **Difference (95% CI)** | **P-Value[1]** | **Interaction P-Value[2]** |
| Popliteal | 13 / 15 (86.7%) | 9 / 9 (100.0%) | -13.3% (-30.5%, 3.9%) | 0.5109 | |

1 Fisher's Exact test for the difference in proportion within subgroup.
2 P-value from the fixed effects logistic regression model treatment by subgroup interaction term. Heterogeneity testing at a p-value<0.15 was prespecified for Gender and Geography.

For the effectiveness endpoint, there were no significant treatment interactions (evaluated at a p value of 0.15) in pre-specified subgroup analyses: male vs female (P=0.8874); US vs OUS (P=0.6560); diabetes vs. no diabetes (P=0.5826); baseline Rutherford Classification, ≤3 vs. >3 (P=0.9386); predilatation method, atherectomy vs. standard balloon angioplasty (P=0.3342); calcification, minimal/none vs. moderate/severe (P=0.2296); lesion length, ≤10 cm vs. >10 cm (P=0.4555); treatment location, hospital vs. outpatient (P=0.9761); target lesion location, SFA vs. popliteal (P=0.9696).

**Table 19. Additional Subgroup Analyses: Primary Effectiveness Endpoint of True DCB Success at 12 Months**

| | #/#(%) | | | | |
|---|---|---|---|---|---|
| **Subgroup** | **Chocolate Touch** | **Lutonix DCB** | **Difference (95% CI)** | **P-Value[1]** | **Interaction P-Value[2]** |
| **Gender** | | | | | 0.8874 |
| Male | 66 / 81 (81.5%) | 52 / 72 (72.2%) | 9.3% (-4.1%, 22.6%) | 0.1836 | |
| Female | 42 / 56 (75.0%) | 36 / 58 (62.1%) | 12.9% (-3.9%,29.8%) | 0.1613 | |
| **Geography** | | | | | 0.6560 |
| US | 31 / 42 (73.8%) | 26 / 45 (57.8%) | 16.0% (-3.6%,35.7%) | 0.1753 | |
| OUS | 77 / 95 (81.1%) | 62 / 85 (72.9%) | 8.1% (-4.2%, 20.4%) | 0.2161 | |
| **Diabetes** | | | | | 0.5826 |
| Diabetes | 44 / 57 (77.2%) | 26 / 43 (60.5%) | 16.7% (-1.5%, 35.0%) | 0.0816 | |
| No Diabetes | 64 / 80 (80.0%) | 62 / 87 (71.3%) | 8.7% (-4.2%, 21.7%) | 0.2114 | |
| **Baseline Rutherford** | | | | | 0.9386 |
| <=3 | 103 / 131 (78.6%) | 82 / 122 (67.2%) | 11.4% (0.5%, 22.3%) | 0.0473 | |
| >3 | 5 / 6 (83.3%) | 5 / 7 (71.4%) | 11.9% (-32.9%, 56.7%) | 1.0000 | |
| **Predilatation** | | | | | 0.3342 |
| Atherectomy | 15 / 17 (88.2%) | 9 / 14 (64.3%) | 23.9% (-5.5%, 53.4%) | 0.1975 | |
| Standard balloon angioplasty | 93 / 120 (77.5%) | 79 / 116 (68.1%) | 9.4% (-1.9%, 20.7%) | 0.1100 | |
| **Calcification** | | | | | 0.2296 |
| Minimal/None | 68 / 84 (81.0%) | 50 / 81 (61.7%) | 19.2% (5.7%, 32.7%) | 0.0093 | |
| Moderate/Severe | 34 / 45 (75.6%) | 27 / 38 (71.1%) | 4.5% (-14.6%, 23.6%) | 0.8034 | |
| **Lesion Length** | | | | | 0.4555 |
| <=10 cm | 36 / 47 (76.6%) | 25 / 43 (58.1%) | 18.5% (-0.6%, 37.5%) | 0.0736 | |
| >10 cm | 72 / 90 (80.0%) | 63 / 87 (72.4%) | 7.6% (-4.9%, 20.1%) | 0.2896 | |
| **Treatment Location** | | | | | 0.9761 |
| *Hospital Based Procedure* | 103 / 132 (78.0%) | 80 / 120 (66.7%) | 11.4% (0.4%, 22.4%) | 0.0484 | |
| *Outpatient Based Lab* | 5 / 5 (100.0%) | 8 / 10 (80.0%) | 20.0% (-4.8%, 44.8%) | 0.5238 | |
| **Location** | | | | | 0.9696 |

| | | | | | |
|---|---|---|---|---|---|
| SFA | 97 / 124 (78.2%) | 81 / 123 (65.9%) | 12.4% (1.3%, 23.5%) | 0.0339 | |
| Popliteal | 11 / 13 (84.6%) | 7 / 7 (100.0%) | -15.4% (-35.0%, 4.2%) | 0.5211 | |

1 Fisher's Exact test for the difference in proportion within subgroup.
2 P-value from the fixed effects logistic regression model treatment by subgroup interaction term. Heterogeneity testing at a p-value<0.15 was prespecified for Gender and Geography.

As noted in the demographics and baseline parameters Section X.C above, minor differences were noted for Lutonix DCB subjects who had greater prevalence of coronary artery disease (CAD) and congestive heart failure (CHF) as compared to Chocolate Touch DCB subjects. Post hoc exploratory subgroup analyses were evaluated and it was determined that there was not a significant interaction between the primary outcomes in either of these subgroups (**Table 20** and **Table 21**).

**Table 20. Exploratory Subgroup Analyses: Primary Effectiveness Endpoint of True DCB Success at 12 Months**

| | #/#%() | | | | |
|---|---|---|---|---|---|
| **Subgroup** | **Chocolate Touch DCB** | **Lutonix DCB** | **Difference (95% CI)** | **P-Value[1]** | **Interaction P-Value[2]** |
| CAD | | | | | 0.5077 |
| CAD | 29 / 40 (72.5%) | 33 / 58 (56.9%) | 15.6% (-3.2%, 34.4%) | 0.1386 | |
| No CAD | 79 / 97 (81.4%) | 55 / 72 (76.4%) | 5.1% (-7.4%, 17.5%) | 0.4476 | |
| CHF | | | | | 0.2463 |
| CHF | 5 / 7 (71.4%) | 10 / 12 (83.3%) | -11.9% (-51.5%, 27.6%) | 0.6027 | |
| No CHF | 103 / 130 (79.2%) | 78 / 118 (66.1%) | 13.1% (2.1%, 24.2%) | 0.0224 | |

[1] Fisher's Exact test for the difference in proportion within subgroup.
[2] P-value from the fixed effects logistic regression model treatment by subgroup interaction term.

**Table 21. Exploratory Subgroup Analyses: Primary Safety Endpoint of Freedom from MAE at 12 months**

| | #/#(%) | | | | |
|---|---|---|---|---|---|
| **Subgroup** | **Chocolate Touch DCB** | **Lutonix DCB** | **Difference (95% CI)** | **P-Value[1]** | **Interaction P-Value[2]** |
| CAD | | | | | 0.0938 |
| CAD | 40 / 44 (90.9%) | 52 / 67 (77.6%) | 13.3% (0.2%, 26.4%) | 0.0775 | |
| No CAD | 88 / 100 (88.0%) | 74 / 82 (90.2%) | -2.2% (-11.3%, 6.8%) | 0.8124 | |
| CHF | | | | | 0.8872 |
| CHF | 8 / 9 (88.9%) | 14 / 17 (82.4%) | 6.5% (-20.8%, 33.9%) | 1.0000 | |
| No CHF | 120 / 135 (88.9%) | 112 / 132 (84.8%) | 4.0% (-4.1%, 12.1%) | 0.3676 | |

[1] Fisher's Exact test for the difference in proportion within subgroup.
[2] P-value from the fixed effects logistic regression model treatment by subgroup interaction term.

*Pharmacokinetic Sub-Study*

A pharmacokinetic subgroup analysis within The Chocolate Touch Study was performed to characterize plasma paclitaxel levels following Chocolate Touch use and calculate the PK parameters in a representative patient cohort. The results from this sub-study help to clearly define the pharmacokinetic profile of paclitaxel delivery in human plasma following treatment with Chocolate Touch. Fifteen (15) subjects were enrolled at two (2) sites in Austria and New Zealand. Blood was sampled at baseline (before treatment), 30min, 1hr, 2hr, 4hr, 8hr, 24hr, and 7days post-treatment. This resulted in bioanalysis of 119 samples, evaluated in multiple runs.

Based on individual data points from the 15 patient PK Cohort, **Table 22** summarizes the

pharmacokinetic parameters including maximum concentration ($C_{max}$), time to maximum concentration ($T_{max}$), area under the curve ($AUC_{0-24h}$) and terminal elimination half-life ($T_{1/2}$) that were calculated using the IV bolus model. Values are the mean of data for all patients. The mean, standard deviation, and the coefficient of variation are reported.

**Table 22. Pharmacokinetic Parameters for Chocolate Touch and Lutonix**

| | $C_{max}$ (ng/mL) | $T_{max}$ (hr) | $AUC_{\infty}$ (hr*ng/ml) | $T_{1/2}$ (hr) | CL (L/hr) | Vz (L) |
|---|---|---|---|---|---|---|
| Mean | 8.21 | 0.53 | 58.9 | 32.0 | 168 | 6250 |
| St. Dev | 4.13 | 0.13 | 26.8 | 18.9 | 71.2 | 2190 |
| % CV | 50.4% | 24.2% | 45.5% | 59.1% | 42.4% | 35.1% |

All Chocolate Touch subjects had detectable plasma paclitaxel immediately after the index procedure that decreased rapidly to less than 2ng/ml within 8 hours. The Chocolate Touch Study met its primary safety endpoint of Freedom from MAE at 12 months, demonstrating non-inferiority of Chocolate Touch to Lutonix DCB with freedom from MAE rates of 88.9% and 84.6%, respectively in the primary ITT analysis set. This finding further supports the safety of the device with the PK profile obtained, with comparable (non-inferior) safety results at 12mo.

*3-Year Mortality Analysis*

Previous meta-analyses of randomized controlled trials of paclitaxel-coated balloons and paclitaxel-eluting stents used to treat peripheral arterial disease in the femoropopliteal arteries have identified an increased risk of late mortality at 2 years and beyond[1,2]. The Chocolate Touch Study was not included in these analyses. The magnitude and mechanism for the increased risk in mortality is currently unclear. Because there is limited follow-up data at 3 years from the Chocolate Touch Study, in order to demonstrate that the Chocolate Touch DCB does not represent an unacceptable risk of late mortality compared to the currently marketed devices, additional analyses were performed.

An analysis was conducted to characterize the long-term mortality profile of the Chocolate Touch device, relative to other FDA-approved paclitaxel-coated devices. This was done by comparison with the active comparator arm of the Chocolate Touch IDE trial, which utilized a commercially available paclitaxel-coated balloon, as well as publicly available data on other commercially available paclitaxel-coated devices.

As of the data freeze date, 140 of the 171 Chocolate Touch subjects (including non-randomized roll-in subjects) had been on study for at least 3 years. **Table 23** displays the counts of death in each year of follow up for the IIT population.

**Table 23. Counts of Death for Annual Follow-Up Periods**

| | ITT Chocolate Touch (N=152) | ITT Lutonix DCB (N=161) |
|---|---|---|
| **1 Year** | 1 | 2 |
| **2 Years** | 4 | 6 |
| **3 Years** | 4 | 7 |

**Table 24** displays Kaplan-Meier estimates in tabular form for the AT population of the IDE Study. The estimated event rates are numerically lower at 1, 2, and 3 years in the Chocolate Touch arm, but confidence intervals overlap at these points, and the survival curves are not significantly different over the 3 years of follow-up (p=0.113, logrank test).

**Table 24. Kaplan-Meier Event Rate Estimates (AT population)**

| | Chocolate Touch (N=171) | | Lutonix DCB (N=160) | |
|---|---|---|---|---|
| | **Rate** | **95% CI** | **Rate** | **95% CI** |
| **1 Year** | 0.006 | (0.001,0.041) | 0.013 | (0.003,0.049) |
| **2 Years** | 0.029 | (0.012,0.069) | 0.052 | (0.026,0.101) |
| **3 Years** | 0.059 | (0.031,0.110) | 0.111 | (0.068,0.179) |
| **Logrank p** | 0.113 | | | |

Kaplan-Meier mortality estimates are provided in tabular form for the ITT analysis set (**Table 25**). The estimated event rates are numerically lower in the Chocolate Touch arm for all years (1, 2, and 3 years). The trial was not adequately powered to detect differences in mortality alone. Survival curves are not significantly different over the 3 years of follow-up (p=0.220, logrank test).

**Table 25. Kaplan-Meier Event Rate Estimates - ITT Analysis Set**

| | Chocolate Touch (N=152) | | Lutonix DCB (N=161) | |
|---|---|---|---|---|
| | **Rate** | **95% CI** | **Rate** | **95% CI** |
| **1 Year** | 0.007 | (0.001,0.046) | 0.012 | (0.003,0.049) |
| **2 Years** | 0.033 | (0.014,0.077) | 0.051 | (0.026,0.100) |
| **3 Years** | 0.067 | (0.035,0.126) | 0.111 | (0.068,0.178) |
| **Logrank p** | 0.220 | | | |

A Bayesian Piecewise Exponential (PWE) survival model fit to the mortality data is summarized in **Table 26**.

**Table 26. Main Predictive Analysis Result**

| | |
|---|---|
| **Predictive Probability that [P($Rate_{3yr}$ < 0.132 \| data)] exceeds 0.95** | 0.999 |

The Bayesian Piecewise Exponential (PWE) survival analysis demonstrated a 0.999 posterior probability that the 3-year mortality rate in subjects treated with the Chocolate Touch device is less than the prespecified performance goal of 0.132 (based on the observed mortality rates of paclitaxel-treated subjects from a patient-level meta-analysis of US IDE randomized controlled trials of paclitaxel coated devices, using the most complete publicly available data set).

Separately, a Bayesian predictive analysis resulted in a 0.999 predictive probability that the 3-year mortality rate in subjects treated with the Chocolate Touch device will be

statistically less than the prespecified performance goal of 0.132 when all study subjects (including 171 total Chocolate Touch subjects) have had the opportunity to reach the 3-year follow-up milestone. The Bayesian predictive analysis demonstrated that the 3-year mortality rate of the Chocolate Touch device is comparable to that of other FDA-approved paclitaxel-coated devices.

4. 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 34 principal investigators (PIs) (and 56 Sub-PIs). None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

# XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

## The ENDURE Early Feasibility Study

### A. Objective

The ENDURE study was a prospective, multi-center, single arm, first in human study designed to provide an initial evaluation of the feasibility, safety, and clinical benefits of the Chocolate Touch (DCC) for the treatment of subjects with infrainguinal arterial disease.

### B. Methods

*Study Design*

The study was planned to enroll up to 100 subjects in Europe and up to 70 subjects in New Zealand. Patients with claudication or ischemic rest pain and angiographically significant lesions (≥70% stenosis) in the superficial femoral and/or proximal popliteal (P1) artery were eligible to participate if they met all inclusion criteria and no exclusion criteria and were willing to provided written informed consent and comply with specified follow-up evaluations.

Angiographic exclusion criteria included severe calcification at the target lesion, primary target lesion within the P2 or P3 segments of the popliteal artery, previous bypass or stent at target vessel or proximal to target vessel, aneurysm in target limb, prior major amputation of target or non-target limb, lesion requiring use of a re-entry device or atherectomy, laser, or ablation procedure, or the use of a drug eluting stent, treatment with another drug coated balloon, or scoring/cutting balloon.

All subjects were treated with the Chocolate Touch device and underwent clinical follow-up at 1, 6 and 12 months, in addition to imaging follow-up: quantitative vessel angiography

(QVA) at 6 months and duplex ultrasound (DUS) at 6 and 12 months.

*Endpoints*

The primary endpoint was target lesion Late Lumen Loss (LLL) at 6 months assessed by quantitative vessel angiography (QVA).

Secondary endpoints included:

- Acute success: device and technical success, bail-out stenting, occurrence and severity of target lesion dissection;
- Clinical: occurrence/severity of device related adverse events; freedom from clinically indicated TLR, major amputation free survival; and clinical improvement (based on Rutherford and ABI changes) at 1, 6 and 12 months;
- Patency: primary and secondary patency at 6 and 12 months.

The primary analysis population for all primary and secondary endpoints was the Intention to Treat (ITT) population, defined as all subjects who provided informed consent and were enrolled in the study.

**C. Results**

*Enrollment and Follow-up*

Between March 18, 2014, and June 29, 2015, a total of 67 subjects were enrolled at 4 investigational sites (one in New Zealand and 3 in Germany). Three subjects enrolled in the study were treated for two target lesions; therefore, the study included a total of 70 target lesions.

All 67 subjects enrolled in the study constituted the ITT population. At 12 months, 61 (91%) subjects had clinical follow up; two subjects were lost to follow-up and one death occurred between 6 and 12 months.

*Baseline Subject and Lesion Characteristics*

The baseline characteristics of the subjects enrolled in the ENDURE study were representative of the lower extremity PAD patient population with above the knee (ATK) lesions. The mean age was 69.2 ± 8.9 years and 61% (41/67) of patients were males. There was a high prevalence of cardiovascular risk factors, including hypertension (87%), hyperlipidemia (68%), diabetes (34%) and smoking (79%). Of the 67 subjects, 20 (30%) had prior coronary interventions (percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)). Most patients, 62/67 (93%) had Rutherford category 3. There were 2 (3%) patients with Rutherford category 4
and 3 (4.5%) patients with Rutherford category 5.

Most lesions, 65/70 (92.9%) were in the superficial femoral artery (SFA). The mean lesion length was 7.3 ± 3.9 cm and the average RVD was 5.2 ± 0.6 mm. Moderate or severe calcification was present in 54.3% (38/70) of cases and 33.3% (23/69) of the lesions were total occlusions. Pre-treatment average minimal luminal diameter (MLD) was 1.2 ± 1.0 mm and %DS was 76.3 ± 19.2%.

*Procedural Characteristics*

On average, 1.4 ± 0.5 Chocolate Touch balloons were used per patient. A single Chocolate Touch device was used in 42 (63%) cases, two in 24 (36%), and three in one case (1%). Pre-dilatation was not required for this study but was recommended for total occlusions and pre-emptively at the discretion of the treating physician. Only 29.9% (20/67) of cases were conducted with pre-dilatation. The DCB was delivered and inflated at the target lesion in 100% of cases. No flow-limiting dissections (Type E or F) were reported after treatment with Chocolate Touch device. Post Chocolate Touch treatment was indicated in 13 cases due to residual stenosis. In one case, the DCC was unable to achieve <50% residual stenosis and bail-out stenting was performed (1/67).

Other post-DCC interventions included stenting that did not meet the pre-defined bailout criteria (n=8) and PTA (n=4).

*Angiographic Outcomes Post Procedure*

Post procedure, mean %DS was 24.4 ± 10.4%, decreased compared with baseline (76.3 ± 19.2%) and mean MLD was 3.8 ± 1.0 mm, increased compared with baseline (1.2 ± 1.0 mm). Postprocedural average acute gain was 2.6 ± 1.1 mm and blood flow was normal in all cases, 100% (69/69).

*Primary Endpoints*

In the ITT population, the primary endpoint of target lesion LLL at 6 months was reported in 52 subjects/54 lesions (78% of subjects [52/67]). The primary endpoint was not reported in 9 cases because the subjects refused angiography. In the ITT population, the average LLL at 6 months was 0.15 ± 0.68 mm (range: -0.31 mm to 1.92 mm). In the PP population, the primary endpoint was reported in 47 patients/47 lesions (77% of subjects [47/61]) and the average LLL was 0.14 ± 0.66 mm.

*Secondary Endpoints - Acute Success*

In the ITT population, the device success rate (per protocol defined as <30% residual stenosis) was 72.9% (51/70 lesions). Technical success, defined as the ability to deliver to and inflate the DCC at the intended target lesion location, was 100% (70/70 lesions). There was one case of bail-out stenting (1.4%, 1/70). No flow-limiting dissection (Type E or F) was reported after treatment with the Chocolate Touch device.

*Secondary Endpoints – Major Adverse Events*

Major Adverse Event (MAE) was defined post-hoc as a composite of clinically-indicated TLR, death and major amputation. At 30 days post-procedure, there were no MAE events (0% [0/67]). Major Adverse Events (MAE) through 12 months in the ITT population are presented in **Table 27**. One death occurred in the study, adjudicated by the CEC as a non-cardiovascular death that was not related to the Chocolate Touch DCC.

**Table 27. ENDURE Major Adverse Events to 12 Months (ITT Population)**

| Secondary Endpoints: Major Adverse Events | Chocolate Touch DCC-ITT population |
|---|---|
| **MAE (%, n/N)** | 9.7 (6/62[a]) |
| Clinically indicated TLR | 8.1 (5/62) |
| Death | 1.6 (1/62) |

| | |
|---|---|
| Major Amputation | 0 (0/62) |
| **Freedom from Clinically Indicated TLR (%, n/N)** | 91.9 (57/62) |
| All TLR (%, n/N) | 9.7 (6/62)[b] |
| **Major Amputation Free Survival (%, n/N)** | 98.4 (61/62) |
| a. The denominator of 62 subjects included 61 subjects with clinical follow-up at 1 year and 1 subject who died prior to 1 year.<br>b. One subject not clinically indicated TLR at 6 months and a clinically indicated TLR at 12 months; therefore, 7 total TLR events were reported. | |

*Secondary Endpoints – Clinical Improvement*

At 1, 6 and 12 months in the ITT population, an ABI increase of ≥0.1 was achieved in 78.6%, 82.7% and 80.0% of patients, respectively. In the ITT population, clinical improvement by ≥1 Rutherford category was 90.5% at 1 month, 93.4% at 6 months and 95.1% at 12 months.

*Secondary Endpoints – Patency*

Primary and secondary patency rates at 6 and 12 months in the ITT population are presented in **Table 28**.

**Table 28. Patency at 6 and 12 Months (ITT Population)**

| | Chocolate Touch DCC ITT Population | |
|---|---|---|
| | 6 months | 12 months |
| **Primary Patency** | 89.3% (50/56) | 80.7% (46/57) |
| **Secondary Patency** | 96.4% (54/56) | 89.5% (51/57) |

## 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 System 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

### A. Effectiveness Conclusions

The Chocolate Touch Study is a prospective, multi-center, randomized controlled trial comparing the Chocolate Touch Paclitaxel Coated PTA Balloon Catheter with the commercially available Lutonix DCB Catheter for the treatment of lesions in superficial femoral or popliteal arteries.

The Chocolate Touch Study met its primary effectiveness endpoint of True DCB Success at 12 months, demonstrating non-inferiority of Chocolate Touch to the Lutonix DCB with True DCB Success rates of 78.8% and 67.7%, respectively ($p_{non\text{-}inferiority} < 0.0001$) in the primary ITT analysis set. Given that non-inferiority of both the safety and effectiveness endpoints were met, a pre-specified superiority analysis for effectiveness of Chocolate Touch to Lutonix DCB was conducted

and met ($P_{superiority}$=0.0386). The imbalance in missing data between treatment groups adds uncertainty to the superiority results. The results of a tipping point analysis demonstrate that the superiority result is not robust. Further, the statistically significant difference in True DCB success between the groups at 12 months was not maintained at 24 months.

## B. Safety Conclusions

The risks of the device are based on non-clinical studies and pre-clinical animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The Chocolate Touch Study also met its primary safety endpoint of Freedom from MAE at 12 months, demonstrating non-inferiority of Chocolate Touch to Lutonix DCB with freedom from MAE rates of 88.9% and 84.6%, respectively ($p_{non\text{-}inferiority}$=0.0001) in the primary ITT analysis set. The rates for MAE components in the Chocolate Touch group vs. the Lutonix DCB group were: target limb related death, 0.8% vs. 0.0%; re-intervention of the target limb, 10.9% vs. 16.3%; major amputation of the target limb 0.0% vs. 0.0%. There were no significant differences between groups with respect to secondary safety endpoints including VIVA safety endpoints, freedom from target limb related MAE, or mortality (low in both groups [0.7% in the Chocolate Touch group vs. 1.3% in the Lutonix DCB group]).

A frequentist analysis of observed mortality rates at 1, 2, and 3 years demonstrated no significant difference in all-cause mortality in the Chocolate Touch group compared with the Lutonix DCB group at all time points in both the ITT and AT analysis sets; the 3-year KM mortality estimate in the ITT analysis set was 6.7% (95% CI, 3.5% to 12.6%) in the Chocolate Touch group and 11.1% (95% CI, 6.8% to 17.8%) in the Lutonix DCB group. Bayesian analyses demonstrated that the 3-year mortality rate of the Chocolate Touch device is comparable to that of other FDA-approved paclitaxel-coated devices.

## C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefit of the Chocolate Touch of improving patient symptoms outweigh the probable risks associated with use of the device. Additional factors to be considered in determining probable risks and benefits include:

1. The clinical study provided adequate follow-up (12 months) to evaluate safety and effectiveness, with measures taken to assess the impact of missing data.

2. The device is intended for use in subjects with peripheral vascular disease of the superficial femoral and popliteal arteries. The results adequately support general use in the identified population.

3. There are alternative treatments available for this disease, such as bare percutaneous transluminal angioplasty (PTA), atherectomy, and stenting.

4. Patient risk is minimized by limiting the use to operators who have the necessary training to use the device safely and effectively. Adherence to the recommended periprocedural medication regimens is also stressed.

5. The frequency and types of the adverse events reported throughout the pivotal clinical study are in alignment with what might be expected in the studied patient population and therapeutic area. No unanticipated adverse device effects were reported in the study.

6. In consideration of the mortality signal observed in patients after 2 years post-treatment with paclitaxel-coated devices used to treat femoropopliteal atherosclerotic disease, long-term Chocolate Touch DCB mortality data was evaluated to demonstrate the Chocolate Touch DCB does not represent an unacceptable risk of late mortality compared to marketed devices.

The probable risks of the device are also based on data collected in clinical studies conducted to support PMA approval as described above. The rates for MAE components in both arms were low and comparable. In the Chocolate Touch group vs. the Lutonix DCB group, the rates of MAE components were: target limb related death, 0.7% vs. 0.0%; re-intervention of the target limb, 10.5% vs. 15.4%; major amputation of the target limb 0.0% vs. 0.0%.

1. Patient Perspectives

   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that, for percutaneous transluminal angioplasty, after appropriate vessel preparation, of lesions up to 180 mm in length in native superficial femoral or popliteal arteries that are appropriate for angioplasty with balloon diameters from 4.0 mm to 6.0 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. The clinical study results are comparable to results from other drug-coated balloons with similar indications. Given all of the available data, it is reasonable to conclude that the benefits of the use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the labeling and Instructions for Use (IFU).

## XIV. CDRH DECISION

CDRH issued an approval order on November 4, 2022. The final conditions of approval cited in the approval order are described below:

1. Long-term drug stability studies will be completed on two total finished product batches representing the commercial process each year, evaluating one lot of the largest-longest device size and one lot of the shortest-smallest device size manufactured during that time period. All batches for these studies will be stored at Long Term Conditions of 25°C ± 2°C/60% RH ± 5%, per ICH Q1A(R2). Testing for all studies will occur at 0, 3, 6, 9, 12, 18, and 24 months, per detailed instruction in document QCI860, Rev. B. Be advised that failure to comply with any post-approval requirement, including test protocol, sampling size, sampling plan, and acceptance criteria, constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(2).

2. The Chocolate Touch Continued Follow-Up Study: This study will evaluate the long-term safety and effectiveness of the Chocolate Touch DCB in 313 subjects from the premarket study (The Chocolate Touch Study). The Chocolate Touch Study was designed as a global, multicenter, single blind, randomized (1: 1 Chocolate Touch DCB to Lutonix DCB) trial. Subjects will be followed annually through 5 years post-procedure, and all efforts must be made to minimize the amount of missing long term data (a minimum of 75% of subjects should be evaluable for the primary efficacy endpoint at 3 years, and a minimum of 90% of subjects should have a documented mortality status at 5 years).

   The primary effectiveness endpoint is true DCB success of the target lesion, defined as a composite of primary patency (peak systolic velocity ratio <2.4 without the need for clinically driven target lesion revascularization) in the absence of a clinically driven bail-out stent (core lab adjudicated).

   The primary safety endpoint is a composite of freedom from major adverse events (MAE), defined as a composite of target limb-related death, major amputation of the target limb, and re-intervention of the target limb.

The endpoints to be assessed through 3 years post-procedure are rate of: (1) major adverse events (MAE), (2) VIVA safety endpoint, (3) true DCB success, (4) clinically-driven target lesion revascularization (CD-TLR), (5) all TLR, (6) primary patency, (7) major amputation, and (8) clinical improvement. Mortality is to be assessed through 5 years post-procedure.

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


1. Food and Drug Administration June 19-20, 2019: Circulatory System Devices Panel of the Medical Devices Advisory Committee. Available Online: https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-19-20- 2019-circulatory-system-devices-panel-medical-devices-advisory-committee-meeting.

2. Katsanos, K., S. Spiliopoulos, P. Kitrou, M. Krokidis, and D. Karnabatidis. 2018. 'Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials', J Am Heart Assoc, 7: e011245.