SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Stent, Carotid
Device Trade Name:	CGuard Prime Carotid Stent System
Device Procode:	NIM
Applicant's Name and Address:	InspireMD, Ltd. Menorat Hamaor 4 Tel Aviv, Israel 67448
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P240029
Date of FDA Notice of Approval:	June 23, 2025

II. INDICATIONS FOR USE

The CGuard Prime Carotid Stent System, when used in conjunction with embolic protection devices specified in the labeling, is indicated for improving carotid luminal diameter in patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet both criteria outlined below:

- Patients with neurological symptoms and ≥50% stenosis of the common or internal carotid artery by angiogram or patients without neurological symptoms and ≥80% stenosis of the common or internal carotid artery by angiogram.
- Patients having a vessel with reference diameters between 6.4mm and 9.0 mm at the target lesion.

III. CONTRAINDICATIONS

The CGuard Prime Carotid Stent System is contraindicated for use in:

- Patients in whom anti-coagulant and/or anti-platelet therapy is contraindicated
- Patients with severe vascular tortuosity or anatomy that would preclude the safe introduction, positioning, support, or proper performance of a guide catheter, sheath, or stent system to allow the effective implant
- Patients with known hypersensitivity to nickel-titanium
- Patients with uncorrected bleeding disorders
- Lesions in the ostium of the common carotid artery

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the CGuard Prime Carotid Stent System labeling.

V. DEVICE DESCRIPTION

The CGuard Prime Carotid Stent System consists of a self-expanding stent composed of nitinol (nickel titanium alloy) and a 6F, 135 cm rapid exchange (Rx) delivery system, shown in Figures 1 and 2, respectively.

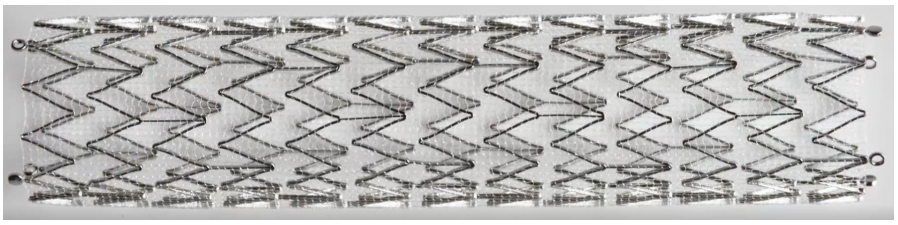


Figure 1: CGuard Carotid Stent

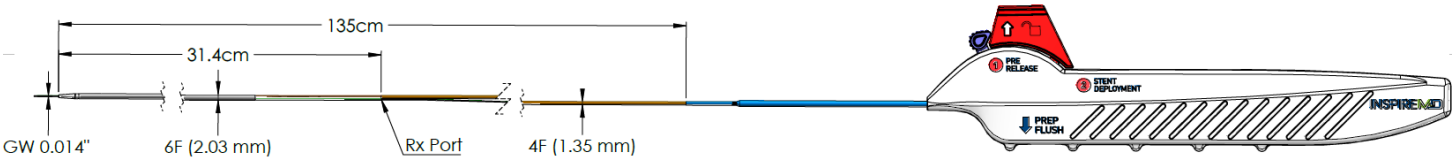


Figure 2: CGuard Prime 135cm Rx Delivery System

The stent is laser cut from solid nitinol tubing into an open-cell stent design formed by circumferential rings that are connected by four peak-to-valley struts. The pattern of stent ring and axial connectors is repeated to achieve the desired stent length. A small-mesh netting (MicroNet®) made from polyethylene terephthalate (PET) is attached to the outside of the stent to act as an embolic filter. The mesh is intended to capture plaque debris and thrombus protrusion through the stent struts and reduce the risk of minor periprocedural ipsilateral stroke associated with carotid artery stenting.

The stent is pre-mounted on a 6F, 135 cm Rx delivery system. The Rx delivery system consists mainly of coaxially arranged inner shaft and outer sheath, and an ergonomic handle. The CGuard Prime stent is constrained within the space between the inner shaft and the outer sheath at the distal end of the delivery system. The delivery system is inserted through a guide catheter or sheath and tracked over the embolic protection device wire or an 0.014" guidewire to the target location where the stent is deployed. Stent deployment is achieved by actuating the lever on the handle, which retracts the outer sheath. A pusher assembly holds the stent in position on the inner sheath while the outer sheath is withdrawn deploying the stent at the target lesion. The deployed stent self-expands and imparts an outward radial force on the arterial wall to establish lumen patency. The stent is intended for straight vessels and is provided in the device sizes listed in Table 1.

Table 1: CGuard Prime Carotid Stent System Catalog Numbers

Referenced Vessel diameter (mm)	Diameter (mm)	Length		Average Foreshortening (%)
		30 mm	40 mm	
6.4-7.3	8.0	CND0830	CND0840	2.6
7.2-8.1	9.0	CND0930	CND0940	1.9
8.0-9.0	10.0	CND1030	CND1040	2.3

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternative practices and procedures for the treatment of carotid artery disease which are dependent on symptomatic status, patient anatomy and comorbidities, and degree of stenosis. Patients with less severe disease or symptoms are generally treated with lifestyle modifications and medical management including antiplatelet and/or anticoagulant medicine, antihypertensive or antilipidemic drugs. Carotid endarterectomy and carotid artery stenting are alternative treatments, particularly with more severe disease. 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 CGuard Carotid Stent System was introduced to the market in February 2014. It has been marketed in the following countries: Argentina; Australia; Austria; Belarus; Belgium; Botswana; Bulgaria; Brazil; Chile; Colombia; Croatia, Cyprus; Czech Republic; Dominican Republic; Aruba; Curacao; Jamaica; Trinidad; Tobago; Denmark; Ecuador; Estonia; Finland; France; Germany; Greece; Hong Kong; Hungary; Iceland; India; Ireland; Israel; Italy; Kazakhstan; Latvia; Liechtenstein; Lithuania; Luxembourg; Macau; Malta; Mexico; Namibia; Netherlands; New Zealand; Norway; Peru; Poland; Portugal; Romania; Russia; Serbia; Slovakia; Slovenia; South Africa; Spain; Sweden; Switzerland; Ukraine; United Kingdom; Vietnam.

The CGuard Stent System has not been withdrawn from marketing for any reason relating to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Abrupt vessel closure
- Allergic reaction (contrast medium; drug; stent or filter material)
- Amaurosis fugax
- Aneurysm or pseudoaneurysm in the vessel or at the vascular access site
- Angina/coronary ischemia

- Arrhythmia (including premature beats, bradycardia, atrial and/or ventricular tachycardia, atrial and/or ventricular fibrillation)
- Asystole or bradycardia
- Arteriovenous fistula
- Bleeding complications from anticoagulant or antiplatelet medication
- Cardiac tamponade
- Cardiogenic shock
- Carotid artery spasm
- Cerebral edema
- Cerebral haemorrhage
- Cerebral ischemia
- Congestive heart failure (CHF)
- Death
- Detachment and/or implantation of a component of the system
- Dissection of blood vessel
- Distal embolic protection device thrombosis and or occlusion
- Emboli (air, tissue, plaque, thrombotic material, stent)
- Emergency artery bypass graft surgery
- Emergent or urgent carotid endarterectomy
- Emergent surgery to remove stent or distal embolic protection device
- Fever
- Hematoma at the vascular access site, with or without surgical repair
- Hemorrhagic event, with or without transfusion
- Hyperperfusion syndrome
- Hypotension/hypertension
- Infection, local or systemic, including bacteremia or septicemia
- Ischemia/ infarction of tissue organ
- Myocardial infarction
- New or worse encephalopathy
- Pain
- Pain at the catheter insertion site
- Pericardial effusion
- Pulmonary edema
- Renal failure/insufficiency
- Respiratory failure
- Restenosis of the stented segment
- Seizure
- Severe unilateral headache
- Stent/embolic protection device entanglement/damage
- Stent/embolic protection device collapse or fracture
- Stent malposition/migration
- Stent thrombosis or occlusion
- Stroke / Cerebrovascular accident (CVA)
- Transient ischemic attack (TIA)

- Tissue necrosis
- Total occlusion of the carotid artery
- Vascular thrombosis/occlusion at the access site, treatment site, or remote site
- Vessel dissection, perforation or rupture
- Vessel spasm or recoil

For the specific adverse events that occurred in the clinical study, please see Section X.D below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A series of non-clinical laboratory and animal studies related to the product were performed to evaluate the device.

A. Biocompatibility Studies

Biocompatibility testing was performed in accordance with the following:

- Good Laboratory Practices (21 C.F.R. §58),
- ISO 10993-1:2018, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process" and
- FDA guidance document "Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems"

Tests were conducted on product manufactured, packaged and sterilized using material and procedures intended for the marketed product for the stent and delivery system. The stent is permanently implanted in the patient's vasculature and therefore has permanent (>30 days) circulating blood contact. The delivery system catheter, which is not implanted, is categorized as external communicating with limited (<24 hours) contact.

Biocompatibility testing demonstrates that the CGuard Prime stent and the delivery system are biocompatible. Table 2 is a summary of biocompatibility testing and results.

Table 2: CGuard Prime Carotid Stent System Biocompatibility Test Summary

Test	Test Description	Stent	Delivery System	Results
Cytotoxicity	ISO MEM Elution Assay w/ L929 Mouse Fibroblast Cells	X	X	Non-cytotoxic
Sensitization	ISO Guinea Pig Maximization Sensitization	X	X	Non-sensitizing
Intracutaneous Reactivity	ISO Intracutaneous Reactivity Test	X	X	Non-irritant
Systemic Toxicity (Acute)	ISO Acute Systemic Injection Toxicity Test	X	X	Non-toxic
Sub-acute, sub-chronic and chronic toxicity	Animal Studies to Evaluate the GCuard Stent System long-term toxicity potential in a porcine model	X	n/a	Non-toxic
Material Mediated Pyrogenicity	USP Rabbit Material Mediated Pyrogenicity Study	X	X	Non-pyrogenic

Test	Test Description	Stent	Delivery System	Results
Genotoxicity	ISO Bacterial Mutagenicity Test - Ames Assay	X	n/a	Non-mutagenic
	ISO In Vitro Mouse Lymphoma with Extended Treatment	X	n/a	
Hemocompatibility	Hemolysis - Direct and Indirect Contact	X	X	Non-hemolytic
	Complement Activation (SC5b-9)	X	X	Non-activator of the complement system
	ISO Thrombogenicity (in vivo) in non-anticoagulated canine	n/a	X	Acceptable thrombogenic performance
	Thrombogenicity (in vivo) 30-day Chronic Porcine Animal Study (in vivo)	X	n/a	Acceptable thrombogenic performance
Chemical Characterization	NVR, LC-MS, GC- MS, and ICP-MS and Toxicological Assessment	X	n/a	Overall assessment demonstrated that the extractables/ leachables are not a concern for subacute/ subchronic/ chronic systemic toxicity, genotoxicity, or carcinogenicity.

B. Engineering Testing

In vitro bench testing to support the CGuard Prime Carotid Stent System was developed based on the device risk assessment and is consistent with the following FDA guidances:

- "Non-Clinical Tests and Recommended Labeling of Intravascular Stents and Associated Delivery Systems", April 18, 2010, and its addendum.
- "Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems", August 18, 2015.

The relevant bench tests outlined in the guidance document and included in support of the CGuard Prime Carotid Stent System are summarized in Table 3 below.

Table 3: CGuard Prime Carotid Stent System Bench Testing

Test	Purpose	Acceptance Criteria	Results
Stent Material Properties			
Material Composition	To verify that the nitinol material composition conforms to the chemical composition requirements of ASTM F2063.	Meets ASTM F2063-18	PASS
Shape Memory & Superelasticity	To verify the correct transition temperature of the nitinol.	Stent shall have an austenite finish (A_f) of 20° ± 3°	PASS
Corrosion Testing	To evaluate the potentiodynamic corrosion resistance of the stent.	N/A Characterization Test	Corrosion resistance and nickel ion release indicate that the stent has an adequate passivation layer.

Test	Purpose	Acceptance Criteria	Results
Nickel Elution	To characterize general/uniform corrosion resistance of the stent.	Stent should exhibit low nickel ion release rate over 60-day period.	The daily Nickel elusion rate per device was less than 0.2 µg and the cumulative elusion over 60 days was less than 0.61 µg.
Stent Dimensional and Functional Attributes			
Dimensional Verification	To verify the stent dimensions post-deployment.	The diameter and length shall meet the labeled specification	Pass
Percent Surface Area	To determine the stent surface area in contact with the vessel.	The percent surface area was calculated for characterization only.	7%-20%
Foreshortening	To verify stent foreshortening.	The implant shall not foreshorten more than 10% from the crimped diameter to the unconstrained diameter.	PASS
Stent Integrity	To verify the ability of the stent to resist delivery-related damage during deployment.	Stent shall be free from the following: • Bare Metal Stent surface defects such as cracks, scratches, buckling or any evidence of stent breakage. • Damage to the inner lumen side • Sleeve Integrity o Sleeve protrusion into the vessel lumen. o Sleeve Integrity (2) torn fibers are allowed. o Three (3) torn fibers are allowed if the torn fibers are distant from each other and cannot be linked to create one larger pore size. o Three (3) torn fibers are allowed if the torn fibers are in the proximal and/or distal crowns.	PASS
Radial Outward Force	To verify the radial outward force of self- expanding stents.	Stent shall meet the following: • Chronic outward force: $\leq$ 1.14N/mm • Radial resistive force $\geq$ 0.1 N/mm	PASS
Finite Element Analysis (FEA)	To characterize the maximum stresses and strains with the device to support fatigue analysis.	N/A Characterization testing.	N/A Characterization only
Fatigue Limit Testing	To determine the safety factor of the stent.	N/A Characterization testing.	The calculated safety factor against fatigue is higher than 3 for all stent sizes.
Accelerated Durability	To verify the stent structural durability under physiologically relevant conditions.	No structure fracture at 10 years of simulated use.	PASS
MRI Safety and Compatibility	To verify the MRI safety and compatibility of the stent.	For characterization purposes only, the conditions under which the device can be safely scanned are determined for product labeling.	Stent is MR Conditional to 1.5 and 3 Tesla.
Radiopacity	To verify the radiopacity of the stent.	The stent must be visible under fluoroscopy.	PASS

<table>
<tr><th>Test</th><th>Purpose</th><th>Acceptance Criteria</th><th>Results</th></tr>
<tr><td>Crush Resistance</td><td>To verify the ability of the stent to recover its desired size and shape after application and removal of external loads.</td><td>All stents must recover from the crushed configuration to 90% of the nominal diameter to assure lumen patency.</td><td>PASS</td></tr>
<tr><td>Kink Resistance</td><td>To verify the kink resistance of the stent when exposed to bending deformation.</td><td>The stent shall accommodate a minimum radius of curvature without kinking or exhibiting a diameter reduction of greater than 50% at a radius of 15mm.</td><td>PASS</td></tr>
<tr><td colspan="4">Delivery System Dimensional and Functional Attributes</td></tr>
<tr><td>Dimensional Verification</td><td>To verify the key dimensions of the delivery system.</td><td>The delivery system shall meet the following design specifications.
<table>
<tr><th>Dimension</th><th>Specification</th></tr>
<tr><td>Usable length</td><td>1350 + 10mm</td></tr>
<tr><td>Outer Sheath Diameter</td><td>≤ 2.04mm</td></tr>
<tr><td>Outer sheath + bi-lumen</td><td>304± 5mm</td></tr>
<tr><td>Guidewire compatibility</td><td>0.014 in GW passes freely</td></tr>
</table></td><td>PASS</td></tr>
<tr><td>Delivery, Deployment and Retraction</td><td>To demonstrate that the delivery systems can safely and reliably deliver the stent to the intended location when tested in an anatomically relevant model.</td><td>The stent shall be prepared per the instructions for use and track to the target location and deploy the stent within in specified accuracy with the specified pre-deployment, deployment, and retraction forces.
<table>
<tr><th>Attribute</th><th>Specification</th></tr>
<tr><td>Flushing</td><td>≤30 sec</td></tr>
<tr><td>Trackability</td><td>Passes</td></tr>
<tr><td>Pushability</td><td>≤10 N</td></tr>
<tr><td>Pre-deployment force</td><td>≤15 N</td></tr>
<tr><td>Deployment force</td><td>≤15 N</td></tr>
<tr><td>Retraction force</td><td>≤10 N</td></tr>
<tr><td>Deploy. Accuracy</td><td>≤ 2.5 mm migration</td></tr>
</table></td><td>PASS</td></tr>
<tr><td>Catheter Bond Strength</td><td>To verify the bond strength of the delivery system bond joints for the intended use</td><td>Catheter bonds shall meet the specified tensile strengths.
<table>
<tr><th>Catheter Bond</th><th>Spec.</th></tr>
<tr><td>Handle to handle adjuster</td><td>≥ 45N</td></tr>
<tr><td>Handle adjuster to stiffener</td><td>≥35N</td></tr>
<tr><td>Stiffener to pusher wire</td><td>≥ 35N</td></tr>
<tr><td>Carriage luer to main shaft prox. assembly</td><td>≥ 45N</td></tr>
<tr><td>Main shaft prox. assembly to main shaft</td><td>≥ 25N</td></tr>
<tr><td>Main shaft to braided out shaft</td><td>≥ 25N</td></tr>
<tr><td>Pusher spiral cut hypotube to pusher wire</td><td>≥ 45N</td></tr>
</table></td><td>PASS</td></tr>
<tr><td>Delivery System Freedom from</td><td>To verify the delivery system is free from fluid leakage when evaluated by flushing</td><td>No leakage of fluids along the delivery system (except from the Rx port and the distal tip connection to the braided shaft)</td><td>PASS</td></tr>
</table>

Test	Purpose	Acceptance Criteria	Results
Leakage	with water and observing for leaks.	shall occur during system flushing for no more than 30 seconds, at pressure of 3bar.	
Tip Pull Test	To determine the tensile force that will separate the distal tip from the catheter.	Tip bond strength shall meet the specified tensile strengths. **Tip Bond Strength** / **Specification** Inner tip to main shaft / ≥ 10N Inner tip to over mold tip / ≥ 10N	PASS
Flexibility and Kink Test	To verify that the delivery system can conform to tortuous target vessels without obstructing the lumen.	Delivery system shall meet a flexed radius of 25mm without kinking or guidewire lumen obstruction.	PASS
Torque Strength	To verify adequate torque strength of the delivery systems when the distal tip is not free to rotate.	The delivery system with stent shall withstand one complete rotation without kink or bond failure. The delivery system after stent deployment withstands ten complete rotations without kink or bond failure. The number of delivery system rotations leading to failure shall be higher than the 10 complete rotations of the catheter.	PASS
Delivery System Internal Diameter	To verify the internal diameter of the delivery system.	Internal diameter ≥1.78mm.	PASS
Particulate Evaluation	To verify the size and diameter of particulate shed by the stent and delivery system.	The stent and delivery system must not shed particulate that exceeds 6000 particles for > 10 µm size and 600 particles for > 25 µm..	PASS
Embolic Protection Compatibility	To verify the system is compatible with the Emboshield NAV Cerebral Protection System and Mo.Ma Ultra Protection Cerebral Protection Device.	The system must be compatible with the Emboshield NAV Cerebral Protection System and Mo.Ma Ultra Proximal Cerebral Protection Device.	PASS

C. Animal Studies

A GLP animal study was performed to evaluate the safety of the CGuard Carotid Stent System, and earlier version of the CGuard Prime Carotid Stent System, in non-diseased swine carotid arteries compared to a commercially available control stent. The animals were divided into two cohorts: 30-day cohort and 90-day cohort. See Table 4 for details.

The results of this study are relevant for the CGuard Prime Stent System since its implanted stent is identical to that included in the CGuard Stent System. The CGuard and CGuard Prime systems have different delivery system and handle designs. The CGuard Prime is equipped with a delivery system which includes a new ergonomic handle designed to facilitate easier stent deployment.

Table 4: CGuard Carotid Stent System Animal Study Summary

Study	A GLP 90-day Animal Study to Evaluate the CGuard Carotid Stent System in a swine model

Purpose	To evaluate the performance and safety of the CGuard Carotid Stent System in the carotid arteries of a swine model as compared to the Wallstent used as Control.

Methods	• Fifteen (15) swine implanted with CGuard stents
	• The animals were divided in two cohorts:
	  o 30-Day - 7 animals (4 test and 3 control) and
	  o 90-Day - 8 animals (5 test and 3 control).
	• On Day 0, angiographic measurements with QVA to guide treatment site selection and vasculature sizing.
	• Bilateral implantations were completed with the Test Articles (CGuard stents) and Control Article (Wallstent) in the right and left carotid arteries according to the cohort treatment group.
	• Prior to termination, angiography with QVA was performed according to the cohort-assigned schedule.
	• Following euthanasia, full necropsy was performed with target, and non-target organs harvested for histopathologic analysis.

Results	• Day 0 implant procedures were successfully performed in all animals, and all animals recovered uneventfully post-operatively. • Thrombogenicity assessment of the delivery systems (30-day animals) post-implantation procedure showed no visible thrombus on any of the delivery systems. • All animals remained clinically healthy throughout the duration of the in-life period and survived to the designated end-point. • Microscopic evaluation of the local (carotid arteries) and downstream (rete mirabilis) tissue response to implantation of the CGuard Stent System in a healthy swine model at 30 and 90 days showed no abnormalities. • The stented vessels were fully healed and widely patent at 30 and 90 days. • The dependent tissues (brain and rete mirabilis) showed neither thromboemboli nor gross evidence of infarction, or vascular compromise. • The test vessels examined via SEM showed a normal morphology and full endothelialization with no thrombosis. • Overall, the CGuard Stent System was very well tolerated and appeared safe based on local and dependent tissue response in the healthy swine model at 30 and 90 days.

D. Packaging Studies and Shelf-Life Testing

Packaging verification testing was performed at non-aged and aged conditions to demonstrate integrity of the packaging is maintained over the 15-month shelf-life of the device. Testing passed pre-determined requirements for visual assessment, dye penetration testing, bubble leak testing, and seal strength testing.

E. Sterilization

The CGuard Prime Carotid Stent System is a sterile single-use device. The device is terminally sterilized using 100% ethylene oxide (EO) gas. In accordance with AAMI/ANSI/ISO 11135:1:2014/AMD. 1:2018, "Sterilization of health-care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices", sterilization testing was performed on the CGuard/CGuard Prime Carotid Stent System to demonstrate that the device can be adequately sterilized to the desired Sterility Assurance Level (SAL) of 10^{-6}. Ethylene Oxide and Ethylene Chlorohydrin residuals meet the requirements of ISO 10993-7:2008/AMD. 1:2019, "Biological evaluation of medical devices Part 7: Ethylene oxide sterilization residuals.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study (C-GUARDIANS) to establish a reasonable assurance of safety and effectiveness of carotid artery stenting with the CGuard Prime Carotid Stent System in patients at high risk for adverse events from carotid endarterectomy (CEA) in the United States (US) and outside the US (OUS) under IDE #G190185. Data from this clinical study are the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between July 22, 2021, and June 23, 2023. The database for this PMA reflected data collected through August 20, 2024, for 317 patients (316 pivotal and 1 roll-in patients) at 24 investigational sites (19 US and 5 OUS sites).

The study was an international, multicenter, single-arm, prospective study to evaluate the safety and effectiveness of the CGuard/CGuard Prime System for the treatment of carotid artery stenosis in subjects with high risk for adverse events from carotid endarterectomy. The CGuard and CGuard Prime Carotid Stent Systems include the same implantable stent and only differ in the design of their delivery systems and handles. Only the CGuard Prime Stent System is the subject of this PMA. The CGuard Stent System was used in 284 patients and the CGuard Prime Stent System in 32 patients. The two device iterations are hereafter referred to as "CGuard Prime."

The primary composite safety and effectiveness endpoint was the incidence of the following Major Adverse Events (MAE): Death (all-cause mortality), all Stroke, and Myocardial Infarction (DSMI) through 30-days post-index procedure, or ipsilateral stroke between 31 and 365 days. All primary endpoint events were adjudicated by the study independent Clinical Event Committee (CEC).

The endpoint was compared to a performance goal (PG) based on published carotid stenting studies selected based on criteria which included high risk for carotid endarterectomy patients, clear categorization of rates for symptomatic and asymptomatic patients and studies associated with previously approved devices. The PG was set to 11.6%. The sample size was determined on enrollment of 25% symptomatic patients and 75% asymptomatic patients and 10% non-evaluable patients at 1-year. Based on these assumptions, an evaluable sample size of 316 subjects provided 80% power to reject the null hypothesis with a one-sided type I error rate of 0.025. The null hypothesis was tested on the ITT population at a one-sided 0.025 level of significance using the one-sided Z-test. If the upper bound of the two-sided 95% confidence interval calculated from the observed primary endpoint rate was < 11.6% and the p-value was less than 0.025, the null hypothesis would be rejected (i.e. performance goal met).

The study had three patient populations: Intent-to-Treat (ITT), modified-ITT (mITT) and Per Protocol (PP). The ITT analysis population includes all enrolled subjects who gave informed consent, who met all eligibility criteria, were approved by the Screening Committee and in whom the study device entered the vasculature. The mITT population was the subset of the ITT analysis population who were implanted with the CGuard Prime

device. The PP population was the subset of the mITT analysis population with no major protocol deviations. Primary endpoint analysis at 1 year is performed on the number of evaluable patients remaining in each population (ITT, mITT, and PP).

Secondary endpoints included technical success, treatment success, the incidence of individual MAE, in-stent restenosis (ISR), target lesion revascularization (TLR), as defined below. Secondary endpoints were descriptive only, with no formal hypothesis testing.

The Data Safety Monitoring Board (DSMB) reviewed all study safety data on a regular basis and advised on the continuing safety, validity and scientific merit of the study. All vascular imaging required for the study was evaluated and analyzed by an independent core lab.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the C-GUARDIANS study was limited to patients who met the following inclusion criteria.

General Inclusion Criteria:

- Subject is ≥ 19 years and ≤ 80 years of age.
- Subject is willing and able to provide appropriate study-specific informed consent, follow protocol procedures, and comply with follow-up visit requirements.
- Subject is willing and able to take dual antiplatelet therapy for a minimum of 30 days.
- Life expectancy ≥ 24 months from the date of the index procedure.
- Females who are not pregnant or lactating and not planning to become pregnant for the duration of the study.
- Subject has a modified Rankin Score of ≤ 2 at the time of informed consent.
- Subject is either:
  - Symptomatic with carotid stenosis ≥ 50%. Symptomatic is defined as amaurosis fugax, transient ischemia attack (TIA) or stroke within the last 6 months ipsilateral to the side of the stenosis.
  - Asymptomatic with carotid stenosis ≥ 80%.

High-risk Inclusion Criteria:

For inclusion in the study, a subject must have qualified in at least one high-risk condition, as shown below.

Co-morbid Conditions:

- Age ≥ 70.
- CCS angina class 3-4 or unstable angina.
- Congestive Heart Failure (CHF) NYHA class III-IV.
- Left ventricular ejection fraction (LVEF) ≤ 35%.
- MI ≥ 72 hours and < 6 weeks pre-procedure.
- Multi-vessel CAD (≥ 2 vessels >70% stenosis) and history of angina.

- Chronic Obstructive Pulmonary Disease (COPD) with FEV1<50.
- Permanent contralateral cranial nerve injury/paralysis.
- Restenosis from previous carotid endarterectomy (CEA).
- Planned coronary artery bypass grafting (CABG) or valve replacement surgery between 31-60 days after CAS.
- Abdominal Aortic aneurysm surgical repair or Endovascular repair is planned between 31 to 60 days after CAS.

Anatomic Conditions:

- Occlusion of the contralateral CCA or ICA.
- Prior radiation treatment to the neck or a radical neck dissection.
- Severe bilateral ICA stenosis requiring treatment.
- Target lesion at or above the level of the jaw (C2) or below the clavicle.
- Severe tandem lesions.
- Inability to extend the neck due to cervical disorders.
- Laryngeal palsy or laryngectomy.
- Prior head and neck surgery in the region of the carotid artery.
- Tracheostomy or tracheostoma.
- Spinal immobility of the neck.
- Hostile neck or surgically inaccessible lesion.

Angiographic General Inclusion Criteria

For inclusion in the study, a subject must have all the following imaging criteria:

- Target lesion location at the carotid bifurcation and/or proximal internal carotid artery (ICA).
- Vessel distal to target lesion can accommodate embolic protection device (EPD) with either the Emboshield NAV6 distal protection device OR the Mo.Ma proximal embolic protection device.
- Diameter at stent landing zone is 4.8 mm to 9.0 mm.
- Target lesion length ≤ 36 mm, that can be covered by a single CGuard Prime Stent.

Patients were <u>not</u> permitted to enroll in the C-GUARDIANS study if they met any of the following exclusion criteria:

- Planned interventional procedure or surgery of the carotid, coronary or peripheral arteries within 30 days before or after the index carotid procedure.
- Severe vascular anatomy that would preclude safe sheath insertion, deliverability of stent or embolic protection device.
- Type III aortic arch.
- Total occlusion of the target vessel.
- Presence of “String sign” of the target lesion.
- In-tandem lesions with ≥ 50% or ≥ 80% diameter stenosis for symptomatic or asymptomatic patients, respectively, which cannot be covered by a single CGuard Prime stent.

- History of bleeding diatheses or coagulopathy.
- Bilateral carotid stenosis requiring treatment on both sides within 30 days prior to or following planned index procedure.
- Subject is on renal replacement therapy or has Stage 4 or 5 Chronic Kidney Disease (CKD).
- Known reason for potential stroke other than carotid artery stenosis, including history of atrial fibrillation or other sources of thromboemboli within the past 12 months.
- History of thrombophilia.
- Known sensitivity or allergy to nitinol or titanium.
- Sensitivity to contrast media that cannot be adequately pre-treated.
- Sensitivity to both forms of protocol-acceptable anticoagulation strategies (i.e., both heparin AND Bivalirudin).
- Sensitivity to an antiplatelet agent AND all protocol acceptable alternative antiplatelet options.
- Previous stent placement in the target vessel.
- Evolving stroke or intracranial hemorrhage, or history of previous intracranial hemorrhage or brain surgery within the past 12 months.
- Major neurologic deficit with NIHSS of ≥ 15.
- Dementia or other neurologic condition confounding the neurologic assessment.
- Clinical condition that, in the opinion of the investigator, makes endovascular therapy impossible or hazardous.
- Subject previously enrolled in this clinical trial.
- Possible/probable non-compliance of subject with protocol required follow up or medication.
- Subject is currently participating in another clinical trial that has not completed its primary endpoint assessment or would confound this C-GUARDIANS Pivotal IDE Clinical Study.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 30 days (-0/+ 7 days), 6 months (± 30 days), 1 year (± 30 days), and 2 and 3 years (± 60 days) postoperatively, as shown in Table 5 below. Adverse events and complications were recorded at all visits.

To determine subject eligibility, a screening committee reviewed imaging data, along with patient medical history, for assessment of inclusion criteria, and approval prior to the study procedure. The screening committee was comprised of an interdisciplinary team of study investigators with pertinent knowledge in carotid stenting. Prior to a subject being enrolled in the study, the investigational site received confirmation from the screening committee that the subject was eligible to be enrolled.

Table 5: Schedule of Events

Test/Assessment	Screening	Baseline	Index Procedure	Discharge or 96 hours post-procedure	30 Day (-0, +7D) (10)	180 Day (± 30D)	1-Year (± 30D)	2- & 3- Year (± 60D)	Unscheduled Visit	Early Withdrawal
Study Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 & 9**	**--**	**--**
Study Consent	X									
Medical History	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X (8)	X (9)
Targeted Physical Exam	X (1)			X	X	X	X	X	X (8)	X (9)
NIH Stroke Scale (2)		X		X	X	X	X	X	X (8)	X (9)
Modified Rankin Scale (mRS)	X (1)				X	X	X	X	X (8)	X (9)
Carotid Duplex Ultrasound	X (3)				X	X	X	X	X (8)	X (9)
Cerebral Angiography or Computed Tomography Angiography (CTA) and Magnetic Resonance Angiography (MRA)	X (4)		X							
Head Computed Tomography or Brain Magnetic Resonance Imaging	X (5)									
Index procedure			X							
12-lead ECG	X (1)			X					X (8)	
Complete Blood Count	X (1)			X					X (8)	
Coagulation Panel/ International normalized ratio for subjects on Vitamin K antagonists	X (1)			X	X	X	X	X	X (8)	X (9)
Chemistry Panel (BUN, Creatinine)	X (1)									
Cardiac Biomarkers (troponins or CK-MB)		X		X (6)						
Pregnancy Test (7)		X								
Adverse Events	X	X	X	X	X	X	X	X	X	X

(1) May be obtained at either Screening or Baseline visit.
(2) Neurological assessment must be performed by a physician or other study team personnel certified in administration of the National Institute of Health Stroke Scale (NIHSS).
(3) Bilateral carotid duplex ultrasound is required within 180 days of the screening visit. The pre-procedure ultrasound is not sent to the core lab.
(4) Cerebral angiography or CTA showing the Internal Carotid Artery (ICA), Common Carotid Artery (CCA) and aortic arch is required 90 days prior to the procedure.
(5) Head CT or Brain MRI is required for symptomatic patients within 180 days of the screening visit.
(6) Routine collection for all subjects at approximately the following post-index procedure intervals: 12-24 hours, 36-48 hours, 72 hours or at discharge. Thereafter, if cardiac biomarkers remain elevated, collect daily until values show a decline.
(7) Urine or serum pregnancy test is acceptable.
(8) To be performed as clinically indicated.
(9) Test/assessments to be performed to the extent possible.
(10) If the CGuard Prime carotid stent system with EPD enters the vasculature and is unsuccessful, a telephone follow-up visit is required at 30 days (+/-7 days).

3. Clinical Endpoints

The primary endpoint is the composite of the incidence of the following Major Adverse Events: Death (all-cause mortality), all Stroke, and Myocardial Infarction (DSMI) through 30-days post-index procedure, or ipsilateral stroke between 31- and 365-day follow-up, based on Clinical Events Committee (CEC) adjudication.

Strokes were defined as acute episodes of local or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Strokes were further categorized as major (NIHSS is ≥ 6 or based on clinical data at least 30 days after the date of stroke onset) or minor (i.e., a non-major stroke). Strokes occurring between 31 and 365 days were considered ipsilateral strokes if involving the anterior circulation (the internal carotid artery, the middle cerebral artery, the anterior cerebral artery, or more proximal intracranial branch of the internal carotid artery) on the same side as the stented carotid artery.

Myocardial infarctions were defined by two methods: the Fourth Universal Definition of MI (UDMI) and the Academic Research Consortium (ARC)-2 definitions. The primary endpoint was analyzed using each definition independently. The primary analysis was conducted using the ARC-2 definition. A sensitivity analysis confirmed similar results using the UDMI definition.

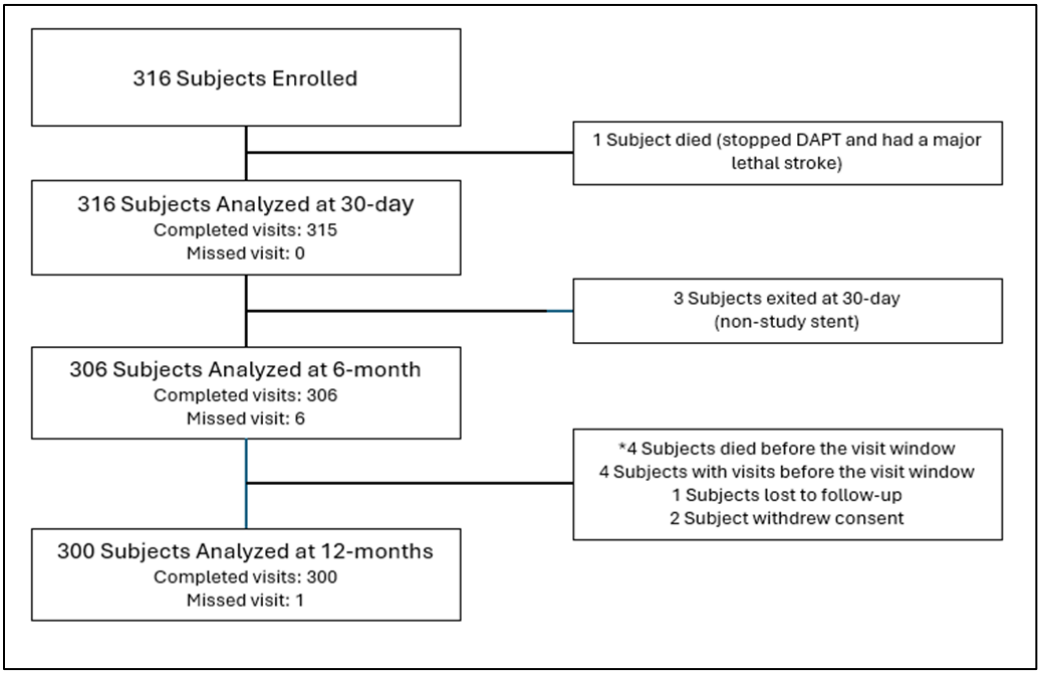
Secondary endpoints included the following:

- Incidence of the following composite of Major Adverse Events: Death (all-cause mortality), all Stroke, and Myocardial Infarction (DSMI) through discharge, 30-days, 6-months, and 1-, 2 -,3-year follow-up, based on CEC adjudication.
- Incidence of each individual component of the Major Adverse Events: Death (all-cause mortality), all Stroke, and Myocardial Infarction (DSMI) through discharge, 30-days, 6-months, and 1-, 2-, 3-year follow-up, based on Clinical Events Committee (CEC) adjudication.
- Ipsilateral stroke through discharge, 30 days, 6 months and 1-, 2-, 3-year follow-up.
- Ipsilateral major stroke through discharge, 30 days, 6 months and 1-, 2-, 3-year follow-up.
- Incidence of In-stent Restenosis (ISR) > 70%. ISR > 70% is defined as PSV > 300 cm/s associated with stent, or vessel occlusion based on transcervical duplex ultrasound through 1-, 2-, 3-year follow-up based on Imaging Core Laboratory assessment and categorized based upon the presence or absence of symptoms associated with restenosis.
- Incidence of In-stent Restenosis (ISR) > 50%. ISR > 50% is defined as PSV > 220 cm/s associated with stent, or vessel occlusion based on transcervical duplex ultrasound, through 1-, 2-, 3-year follow-up evidenced by Imaging Core Laboratory assessment and categorized based upon the presence or absence of symptoms associated with restenosis.

- Incidence of Target Lesion Revascularization (TLR) through 1-, 2-, 3-year follow-up. TLR is defined as clinically driven revascularization procedure of the original treatment site, including angioplasty, stenting, endarterectomy, or thrombolysis, performed to open or increase the luminal diameter within the stented lesion or within 5 mm proximal or distal to the index stent.
- Ipsilateral stroke, stent thrombosis, cardiovascular death or other device related clinical events from discharge up to 1-, 2-, and 3-year follow-up.
- Primary endpoint for subjects that adhere to antiplatelet pharmacology.
- Technical Success defined as the number of subjects with at least one study stent that is successfully delivered and deployed with final residual diameter stenosis < 30% following final post-balloon dilatation, if performed. Based on quantitative angiography measurements at time of index procedure.
- Treatment Success defined as the number of subjects who meet Stent Technical Success without experiencing a Major Adverse Event (based on Clinical Events Committee (CEC) adjudication) through 30-day, divided by the total number of subjects where stent deployment was attempted.

4. Accountability of PMA Cohort

At the time of database lock, of 316 patients enrolled in the PMA pivotal study, 94.9% (n=300) were available for ITT analyses at 12-months. A summary of subject disposition per ITT Analysis is presented in Figure 3.



*Four (4) subjects died between 31 days and the opening of the 12-month visit window and were therefore not evaluable for analysis at 12-month in the ITT analysis.

Figure 3: Subject Disposition per ITT Analysis

The primary analysis of safety and effectiveness was based on the ITT population of 316 subjects with 300 patients with evaluable primary endpoint information through 1 year.

Of the ITT analysis population of 316 subjects, 16 subjects were not included in the primary endpoint proportion. The reasons for these subjects not being included are the following: three (3) study device not implanted and subsequently exited the study at 30 days, one (1) lost to follow-up prior to 1 year follow-up, two (2) withdrew informed consent prior to 1 year follow-up, two (2) 12-month visit not performed and subject not yet exited, four (4) 12-month visit performed prior to window open and no subsequent visit performed, and four (4) deaths occurred between 31 days and the 12-month visit window opening (day 335).

Of the mITT analysis population of 313 subjects, thirteen (13) subjects were not included in the primary endpoint proportion. The reasons for these subjects not being included are the following: one (1) lost to follow-up prior to 1 year follow-up, two (2) withdrew informed consent prior to 1 year follow-up, two (2) 12-month visit not performed and subject not yet exited, four (4) 12-month visit performed prior to window open and no subsequent visit performed, and four (4) deaths occurred between 31 day and the 12-month visit window opening (day 335).

Of the PP analysis population of 295 subjects, nine (9) subjects were not included in the primary endpoint proportion. The reasons for these subjects not being included are the following: one (1) lost to follow-up prior to 1 year follow-up, one (1) withdrew informed consent prior to 1 year follow-up, three (3) 12-month visit performed prior to window open and no subsequent visit performed, and four (4) death occurred between the 31 day visit window opening (day 335).

B. Study Population Demographics and Baseline Parameters

1. Patient demographics

The ITT study population was predominantly male (64%) and Caucasian (97%). Median age was 70 years. Subject demographics are summarized in Table 6. The demographics of the study population are typical for a carotid artery stenting study performed in the US.

Table 6: Subject Demographics

Subject Demographics	ITT (N = 316)
Sex	
Female	36.1% (114)
Male	63.9% (202)
Age	
Mean ± SD	69.0 ± 6.6
Median	70.0
Min, Max	47, 80
Race	
American Indian or Alaska Native	0.3% (1)
Asian	0.0% (0)
Black or African American	1.9% (6)
Native Hawaiian of Other Pacific Islander	0.3% (1)
Caucasian	97.2% (307)
Other	0.3% (1)
Ethnicity	
Hispanic or Latino	10.1% (32)
Not Hispanic or Latino	88.3% (279)
Unknown	1.6% (5)
Current Alcohol Use	
None	72.5% (229)
≥1 drinks/week	27.5% (87)
Smoking History	
Never Smoked	26.6% (84)
Current Smoker	26.3% (83)
Former Smoker	47.2% (149)

2. Subject Medical History

A summary of subject medical history is provided in Table 7. A total of 79 subjects (25.0%) were reported to be symptomatic. All subjects were high-risk for carotid endarterectomy, with 159 subjects (50.3%) being high risk for anatomic reasons, 220 subjects (69.6%) for medical history (comorbidity) reasons. Sixty-three (63) subjects (19.9%) were high risk for both anatomic and comorbidity reasons. One hundred thirty-two (132/316, 41.8%) subjects were diabetics, 53.2% had a history of coronary artery disease, 24.7% a history of MI and 24.1% had COPD. A vast majority of patients had hypertension (93%) and dyslipidemia (90%). Fourteen (14) subjects had a history of atrial fibrillation (AF). Of these 14, three (3) subjects had ongoing AF at the time of enrollment.

Table 7: Subject Medical History

Subject Medical History	ITT (N = 316)
Alzheimer's Disease	0.0% (0/316)
Diabetes Mellitus	41.8% (132/316)
Angina	21.2% (67/316)
Cardiac Arrhythmia	10.1% (32/316)
Atrial Fibrillation	4.4% (14/316)
Congestive Heart Failure	7.0% (22/316)
Chronic Obstructive Pulmonary Disease	24.1% (76/316)
Coronary Artery Disease	53.2% (168/316)
Previous PCI	33.9% (107/316)
Hypercholesterolemia / Dyslipidemia	89.9% (284/316)
Hypertension	93.0% (294/316)
Peripheral Vascular Disease	30.1% (95/316)
Myocardial Infarction	24.7% (78/316)
Stroke	22.2% (70/316)
Transient Ischemic Attack	13.0% (41/316)
Amaurosis Fugax	13.3% (42/316)
Previous Carotid Intervention at the target vessel	5.1% (16/316)
Symptomatic	25.0% (79/316)
High risk for CEA	100% (316/316)
High risk for CEA due to anatomic condition	50.3% (159/316)
High risk for CEA due to comorbidity	69.6% (220/316)
High risk for CEA due to both conditions	19.9% (63/316)

3. Lesion Characteristics

Lesion characteristics as determined by an independent core lab are summarized in Table 8 below. The mean lesion length was 18.6 mm, with moderate to severe calcification reported in approximately 35% of them. The mean pre-procedure target lesion percent stenosis was 90.2%.

Table 8: Lesion Characteristics (Core Lab)

Lesion Characteristics	ITT (N = 316)
Target Lesion Side	
Left	51.0% (159/312*)
Right	49.0% (153/312)
Calcification[#]	
None/Mild	64.3% (200/311**)
Moderate	20.6% (64/311)
Severe	15.1% (47/311)
Lesion length (mm)	
N	308***
Mean ± SD	18.6 ± 7.3
Median	18.0
Min, Max	2.2, 44.1
Minimum Lumen Diameter (mm)	
N	308
Mean ± SD	1.0 ± 0.6
Median	0.9
Min, Max	0.1, 3.2
Reference Lumen Diameter (mm)	
N	308
Mean ± SD	4.0 ± 0.7
Median	4.0
Min, Max	1.0, 6.8
Stenosis (%)	
N	311
Mean ± SD	90.2 ± 9.7
Median	93.0
Min, Max	53.0, 100.0

*Four (4) ITT subjects did not have Core Lab target lesion side reported,
**One (1) additional patient also did not have calcification and stenosis reported and
***An additional three (3) subjects did not have lesion length, minimum lumen diameter and reference lumen diameter reported.
#Two views were used to assess calcification. In the event that the two views reported different calcification, the most severe calcification were reported. Calcification Scoring System: None/Mild: No visualized radiopacities noted in target lesion (TL) / Moderate: Radiopacities noted in TL that are non-circumferential / Severe: Radiopacities noted in TL that are circumferential.

4. Procedure Characteristics

A summary of procedure outcomes is provided in Table 9. The mean residual stenosis at the completion of the study procedure was 7.2%. At least half of the lesions had 0%

stenosis at the end of the procedure (median = 0%). Embolic protection of the target vessel was mandatory per protocol (100% performed). Preclinical testing supported the compatibility of the CGuard Prime Stent System with either the Emboshield NAV6 or Mo.Ma embolic protection devices (EPDs). The clinical protocol allowed for the investigator to choose between these two EPD options. Some investigators chose to use two (i.e., both Emboshield Nav 6 and Mo.Ma Ultra)EPDs during the procedure per their common practice. Emboshield NAV6 alone was used in 237 subjects, 54 subjects had Mo.Ma Ultra alone, 24 subjects had Emboshield NAV6 and Mo.Ma used together, and a non-study EPD (Filterwire EZ) was used for one subject due to the unavailability of any of the protocol required EPD at the time of procedure. Three (3) subjects received a non-study stent, while six (6) other subjects were implanted with 2 study stents.

Table 9: Procedural Characteristics

Procedural Characteristics	**ITT (N = 316)**
Balloon Pre-dilation Performed	
No	7.0% (22/316)
Yes	93.0% (294/316)
Balloon Post-dilation Performed	
No	3.2% (10/316)
Yes	96.8% (306/316)
Embolic Protection Device	100.0% (316/316)
Emboshield NAV6 alone	75.0% (237/316)
Mo.Ma Ultra alone	17.1% (54/316)
Both EPDs	7.6% (24/316)
Non-study EPDs	0.3% (1/316)
Post-procedure stenosis (%)	
N	302
Mean ± SD	7.2 ± 11.9
Median	0.0
Min, Max	0.0, 62.0
Study stents implanted	319
Size 8x30 mm	27/319 (8.6%)
Size 9x30 mm	38/319 (12.1%)
Size 10x30 mm	63/319 (20.1%)
Size 8x40 mm	41/319 (13.1%)
Size 9x40 mm	53/319 (16.9%)
Size 10x40 mm	97/319 (31.0%)
Non-study stents implanted	3
More than one study stent implanted	6

C. Safety and Effectiveness Results

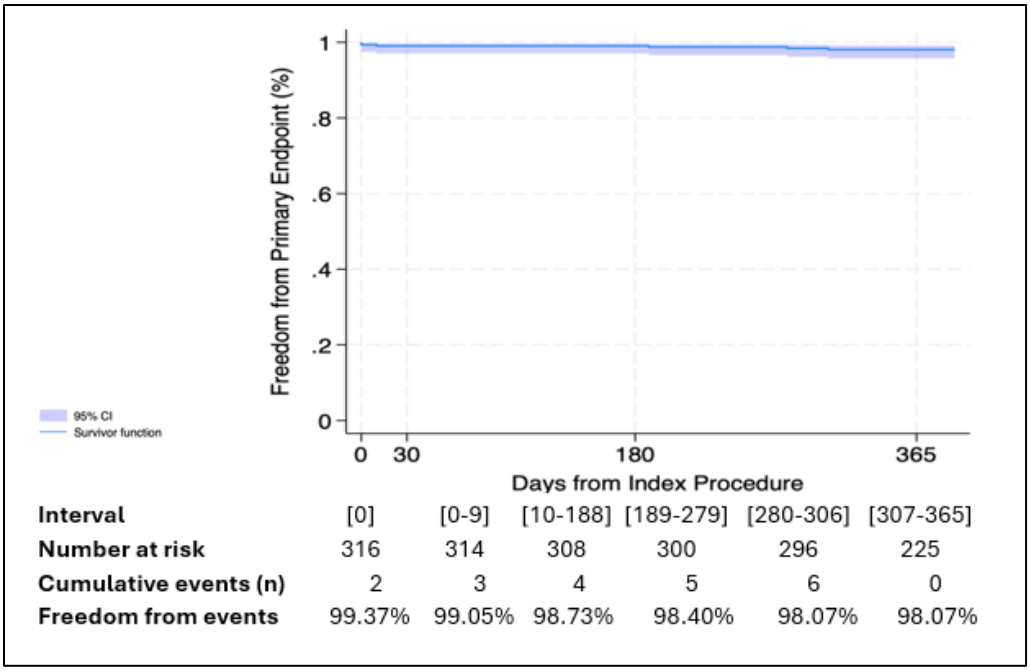
1. Primary Safety and Effectiveness Results

The primary analysis of safety and effectiveness was based on the ITT population of 316 subjects with 300 patients with evaluable primary endpoint information through 1 year. The primary endpoint was defined as the incidence of the following Major Adverse Events: Death (all-cause mortality), all Stroke, and Myocardial Infarction (DSMI) through 30-days post-index procedure, or ipsilateral stroke between 31 and 365 days. All primary endpoint events were adjudicated by the study independent Clinical Event Committee (CEC).

Three (3) subjects (0.95%) had one or more MAEs through 30 days post-index procedure. Of those MAEs, two (2) were due to a minor stroke, and one (1) was due to a major stroke and resulted in death at day 10 in a subject who stopped DAPT, a major protocol deviation. Three (3) subjects (1.00%) had an ipsilateral stroke between 31- and 365-days post-index procedure. Of those, two (2) were major and one (1) was minor.

The binary MAE proportion at 1-year was 2.00% (6/300) for the ITT population. The corresponding one-sided 95% upper confidence limit (UCL) for the MAE proportion was 4.3%, substantially lower than the pre-specified performance goal of 11.6%. The binomial test of the binary MAE proportion demonstrated that the study met the performance goal of 11.6% with a significant one-sided p-value < 0.001. The binary MAE proportions were concordant in the mITT and PP populations, with MAE rates through 1-year of 2.00% and 1.75%, respectively. No hypothesis testing was performed on the mITT or PP populations.

Pre-specified Kaplan-Meier estimates analyses were performed for the primary endpoint. No hypothesis testing was performed. Following the index procedure, 98.06% of treated patients were free of death, stroke or MI (DSMI) at 30 days or ipsilateral stroke between 31 and 365 days in the ITT population. The Kaplan-Meier estimate for the primary endpoint rate is 1.93% in the ITT population (Figure 4). The Kaplan-Meier estimates in the mITT and PP populations were comparable at 1.94% and 1.71%, respectively.



Interval	[0]	[0-9]	[10-188]	[189-279]	[280-306]	[307-365]
Number at risk	316	314	308	300	296	225
Cumulative events (n)	2	3	4	5	6	0
Freedom from events	99.37%	99.05%	98.73%	98.40%	98.07%	98.07%

Kaplan-Meier curve shows freedom from perioperative composite and ipsilateral stroke between 31 days and 1 year. The overall composite event-free rate is 98.07% at 1year. Brackets denote the beginning and end of intervals. Number at risk represents the number of patients at risk of events at the end of each interval. Number of events are cumulative.

Figure 4: Kaplan-Meier estimate - Primary Endpoint (ITT)

2. Secondary Endpoints Results

Secondary endpoint results were descriptive in nature without any formal statistical hypotheses testing.

Major Adverse Event Rates

Table 10 and Table 11 present the cumulative individual MAE number of events and rates through discharge, 30-day, 6-month and 1-year, as well as the rates for each individual MAE and for the composite of DSMI at the same timepoints in the ITT and PP populations, respectively.

Table 10: MAE Composite Rate (DSMI) and Individual Rates (ITT)

MAE	ITT Population (N=316)			
	Discharge	30-day	180-day	1-year
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Death, Stroke, MI	2/316 (0.6%)	3/316 (0.9%)	5/316 (1.6%)	15/316 (4.7%)
Death (all cause)	0	1/316 (0.3%)	1/316 (0.3%)	7/316 (2.2%)
Stroke	2/316 (0.6%)	3/316 (0.9%)	5/316 (1.6%)	9/316 (2.8%)
Myocardial Infarction	0	0	0	0
Ipsilateral Stroke	1/316 (0.3%)	2/316 (0.6%)	2/316 (0.6%)	5/316 (1.5%)
Major Ipsilateral Stroke	0	1/316 (0.3%)	1/316 (0.3%)	3/316 (0.9%)

Table 11: MAE composite rate (DSMI) and individual rates (PP)

MAE	PP Population (N=295)			
	Discharge	30-day	180-day	1-year
	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Death, Stroke, MI	2/295 (0.7%)	2/295 (0.7%)	3/295 (1.0%)	12/295 (4.1%)
Death (all cause)	0	0	0	5/295 (1.7%)
Stroke	2/295 (0.7%)	2/295 (0.7%)	3/295 (1.0%)	7/295 (2.4%)
Myocardial Infarction	0	0	0	0
Ipsilateral Stroke	1/295 (0.3%)	1/295 (0.3%)	1/295 (0.3%)	4/295 (1.4%)
Major Ipsilateral Stroke	0	0	0	2/295 (0.7%)

Kaplan-Meier estimates for these time-to-event endpoints yielded similar results. At 1-year the K-M estimates for the ITT and PP populations are as follow (Table 12):

Table 12: K-M estimates for MAE component rates through 1-year (ITT and PP)

K-M estimates	ITT	PP
Death (all cause)	2.3%	1.7%
Stroke	2.9%	2.4%
Myocardial Infarction	0	0
Ipsilateral Stroke	1.6%	1.4%

Sensitivity Analyses

Tipping point analysis

A tipping point analysis using the ITT population for the primary endpoint was performed, where patients with missing data are considered failures, one at a time, until the primary endpoint null hypothesis is not rejected. Using a binomial test, the tipping point sensitivity analysis demonstrated that the primary endpoint outcomes were robust with a value of 6.96% (22/316) with a 95% CI of (4.41%, 10.35%), as shown in Table 13. Even with all missing data considered as failure, the null hypothesis was rejected.

Table 13: Tipping Point Analysis (ITT)

	Proportion (n/N), 95% CI	**Binomial test p-value**
Primary Endpoint – missing data imputed as failure	6.96% (22/316), (4.41%, 10.35%)	0.005

Sensitivity analysis using the UDMI for periprocedural MI events

A sensitivity analysis was performed using the UDMI for periprocedural MI events, for primary objective analysis and for the first two secondary objective analyses that involve DSMI endpoints. There was no difference in outcome of the primary endpoint when using the UDMI definition of MI in the analysis.

Multiple imputations

For the primary analysis, missing data was imputed using multiple imputation methods. A total of 50 imputations were carried out for the primary endpoint. The imputed primary endpoint rate in the ITT population was 2.39%, with an upper bound 95% CI of 4.25%, well below the Performance Goal of 11.6%.

Poolability of Sites

Consistency of the primary endpoint between sites with 5 or more subjects was evaluated using the Fisher's exact test resulting in a p-value = 0.4865. Data from sites was therefore considered poolable.

In-stent restenosis through 1-year as determined by Core lab

Incidence of In-stent Restenosis (ISR) is determined via transcervical duplex ultrasound imaging assessed by the Core lab. ISR > 70% is defined as PSV > 300 cm/s associated with stent, or vessel occlusion, and ISR > 50% is defined as PSV > 220 cm/s associated with stent, or vessel occlusion. The percent diameter stenosis at 1-year is summarized in Table 14. For those subjects with a 1-year image, 7.0% had >50% stenosis and 2.5% had >70% restenosis in the mITT population (implanted with the study stent).

Table 14: In-stent Restenosis (mITT) per Core lab at 1-year

	mITT (N = 313) Proportion (n/N), (95% CI)
In-Stent Restenosis > 70%	2.5% (7/284*), (1.0%, 5.0%)
Symptoms associated with restenosis	0.4% (1/284), (0.0%, 1.9%)
In-Stent Restenosis > 50%	7.0% (20/284), (4.4%, 10.7%)
Symptoms associated with restenosis	0.4% (1/284), (0.0%, 1.9%)
Vessel Occlusion	0.7% (2/292**), (0.1%, 2.5%)

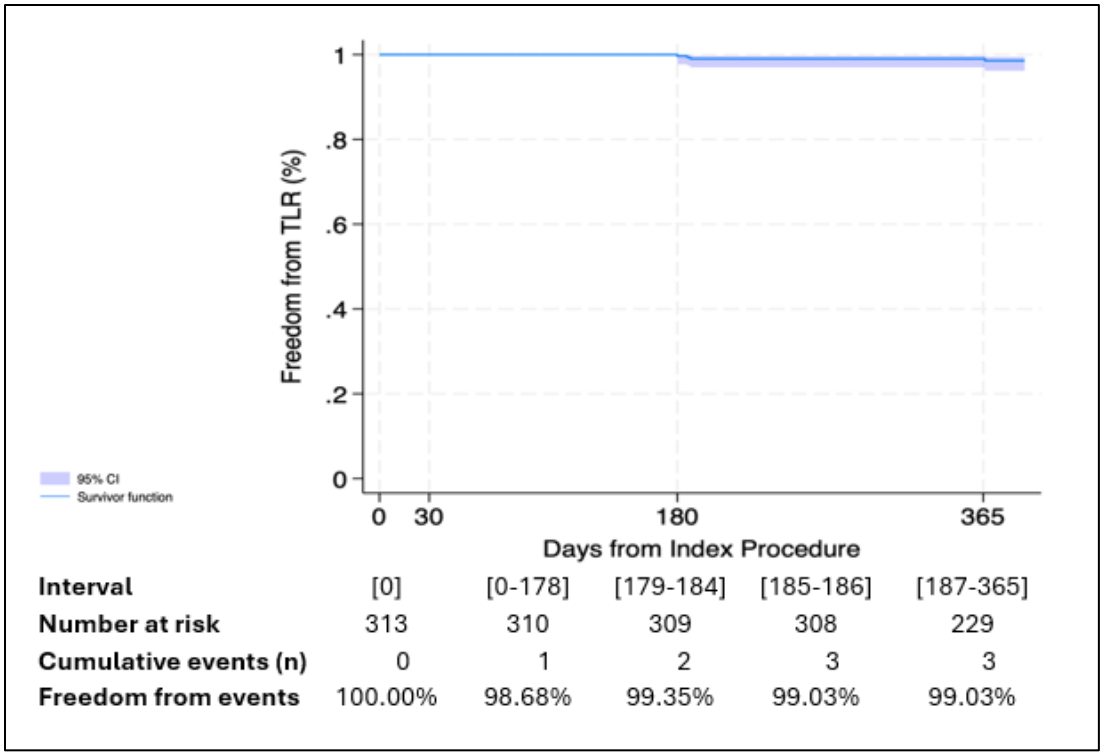
* The denominator of 284 includes those mITT subjects that had a core lab reported maximum peak systolic velocity (PSV) in-stent and available stent patency at 1-year.
** Vessel occlusion is based on stent patency available at 1-year.

Target Lesion Revascularization (TLR) through 1-year

TLR was defined in the protocol as revascularization procedure of the original treatment site, including angioplasty, stenting, endarterectomy, or thrombolysis, performed to open or increase the luminal diameter within the stented lesion or within 5 mm proximal or distal to the index stent.

Clinically driven Target Lesion Revascularization (CD-TLR) was further defined as any surgical or percutaneous revascularization of the target lesion and associated with symptoms (amaurosis fugax, transient ischemia attack (TIA) or stroke ipsilateral to the side of the stenosis) or a narrowing of >80% using NASCET criteria by Core lab. This includes repeat angioplasty, stenting, endarterectomy or extracranial-intracranial bypass.

Three (3) patients were adjudicated as having a TLR during the one-year period in the mITT population. Subjects were required to either have an event of interest (TLR) within 1-year, or at least 335 days of follow up to be included in the analysis. The binary TLR rate at 1-year was 1.0% (3/299) with a 95% CI (0.2%, 2.9%). All 3 subjects were treated with a non-study stent placed within the study stent. All 3 TLR subjects were asymptomatic, but Core lab angiographic results revealed a >80% stenosis for one subject CG-001-035, meeting the definition of CD-TLR. The overall CD-TLR rate at 1-year was 0.3% (1/299).
Freedom from TLR at 1-year by Kaplan-Meier Analysis was 99.03% in the mITT population (Figure 5).



Interval	[0]	[0-178]	[179-184]	[185-186]	[187-365]
Number at risk	313	310	309	308	229
Cumulative events (n)	0	1	2	3	3
Freedom from events	100.00%	98.68%	99.35%	99.03%	99.03%

Kaplan-Meier curve shows freedom from TLR between procedure day and 1 year. The overall event-free rate is 99.37% at 1 year. Brackets denote the beginning and end of intervals. Number at risk represents the number of patients at risk of events at the end of each interval. Number of events are cumulative.

Figure 5: Freedom from TLR (mITT)

Prespecified Site Reported Device Related Events Discharge through 1-year

Incidences of ipsilateral stroke (e.g., major and minor), stent thrombosis, cardiovascular death as adjudicated by the CEC, and other pre-specified device related clinical events as reported by the sites, are summarized for the ITT population in Table 15.

Table 15: Prespecified CEC and Site Reported Device Related Events through 1-year

	ITT (N= 316)	
	AEs (n)	**Subjects n (%), (95% CI)**
Adjudicated by CEC		
Ipsilateral Stroke	4	4 (1.3%), (0.3%, 3.2%)
Stent Thrombosis	1*	1 (0.3%), (0.0%, 1.8%)
Cardiovascular Death	3	3 (0.9%), (0.2%, 2.7%)
Site reported		
Other Device Related Events		
Carotid artery occlusion	1*	1 (0.3%), (0.0%, 1.8%)
Carotid artery stenosis	1	1 (0.3%), (0.0%, 1.8%)
Claudication of jaw muscles	1	1 (0.3%), (0.0%, 1.8%)
Dysarthria	1	1 (0.3%), (0.0%, 1.8%)
Headache	1	1 (0.3%), (0.0%, 1.8%)
Neck pain	1	1 (0.3%), (0.0%, 1.8%)
Pain in jaw	1	1 (0.3%), (0.0%, 1.8%)
Vascular Stent occlusion*	2	2 (0.3%), (0.0%, 1.8%)
Vascular Stent stenosis	3	3 (0.9%), (0.0%, 1.8%)

* This subject is counted twice in Table 15 as a site-reported carotid artery occlusion and as an adjudicated stent thrombosis by the CEC.

Technical and Treatment Success

Technical Success was defined as the number of subjects with at least one CGuard Prime device successfully delivered and deployed with final residual diameter stenosis <30% based on quantitative angiography measurements at the end of the index procedure. Technical success was achieved in 91.7% of the ITT population (278/303); twenty-two (22) failures to achieve technical success were due to final diameter residual stenosis ≥30% and three (3) to non-deployment.

The CGuard Prime Treatment Success Rate was defined as the number of subjects with Technical Success and who did not experience any Major Adverse Event based on CEC adjudication through 30 Days. Treatment Success was achieved in 90.8% (275/303) of the ITT population as 3 subjects experienced a stroke within 30 days, one of which was adjudicated as a major ipsilateral stroke and death (Table 16).

Table 16: CGuard Prime Technical and Treatment Success

	ITT (N = 316) Proportion (n/N), (95% CI)	**Per Protocol (N = 295)** Proportion (n/N) (95% CI)
Technical Success	91.7% (278/303*) (88.1%, 94.6%)	93.0% (264/284**) (89.3%, 95.6%)
Treatment Success	90.8% (275/303*) (86.9%, 93.8%)	92.3% (262/284**) (88.5%, 95.1%)

*Post-intervention imaging to determine stenosis percent was not available from the core lab for 13 ITT subjects. These subjects were not included in the assessment of technical and treatment success.
** Post-intervention imaging to determine stenosis percent was not available from the core lab for 11 PP subjects. These subjects were not included in the assessment of technical and treatment success.

As a post-hoc analysis, the sponsor performed an analysis of technical success defined as the number of subjects with at least one CGuard Prime device successfully delivered and deployed with final residual cross-sectional area stenosis <50% based on quantitative angiography measurements at the end of the index procedure as assessed by the Core Lab, divided by the number of patients with attempted implant of the CGuard stent in the ITT population. Technical success was achieved in 98.3% of the ITT population (298/303); two failures to achieve technical success were due to final residual cross-sectional stenosis ≥50% and three to non-deployment.

Treatment Success, per the post-hoc analysis, was achieved in 97.4% (292/303) of the ITT population as three (3) subjects experienced a stroke within 30 days, one of which was adjudicated as a major ipsilateral stroke and death (Table 17).

Table 17: CGuard Prime Technical and Treatment Success (Post-hoc Analysis)

	ITT (N = 316) Proportion (n/N), 95% CI	**Per Protocol (N = 295)** Proportion (n/N) (95% CI)
Technical Success	98.3% (298/303*) (96.2%, 99.5%)	99.3% (282/284**) (97.5%, 99.9%)
Treatment Success	97.4% (295/303*) (94.9%, 98.9%)	98.6% (280/284**) (96.4%, 99.6%)

*Post-intervention imaging to determine stenosis percent was not available from the core lab for 13 ITT subjects. These subjects were not included in the assessment of technical and treatment success.
** Post-intervention imaging to determine stenosis percent was not available from the core lab for 11 PP subjects. These subjects were not included in the assessment of technical and treatment success.

3. Adverse Events

An Adverse Event (AE) was defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. (ISO 14155:2020)
A Serious Adverse Event (SAE) was defined as Adverse Event that led to any of the following:

1. Death
2. Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    a. a life-threatening illness or injury
    b. a permanent impairment of a body structure or a body function, including chronic disease, or
    c. in-patient or prolonged of an existing hospitalization, or
    d. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function, fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment. (ISO 14155:2020).

A planned hospitalization for a pre-existing condition was not considered a SAE.
An Adverse Device Effect (ADE) was defined as an Adverse Event related to use of an investigational medical device.

An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21CFR 812.3)

An Unanticipated Serious Adverse Device Effect (USADE) is defined as a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. (ISO 14155:2020)

As shown in Table 18, of the 316 subjects, 115 (36.4%) subjects experienced an adverse event through the 30-day follow-up, and 193 (61.1%) subjects experienced an adverse event through the 12-month follow-up. Thirty-seven (37) subjects (11.7%) experienced a serious adverse event through the 30-day follow-up, and 102 (32.3%) subjects experienced a serious adverse event through the 12-month follow up. No unexpected adverse device events (UADE) or unexpected serious adverse device events (USADE) were observed in any subject.

Table 18: Summary of all AEs on or after the procedure through 365 days post-procedure (ITT)

System Organ Class Preferred Term	Number of events	Number (%) of Subjects
Total	**497**	**193 (61.1%)**
Blood and lymphatic system disorders	**7**	**7 (2.2%)**
Anaemia	6	
Leukocytosis	1	
Cardiac disorders	**72**	**49 (15.5%)**
Acute myocardial infarction	14	
Atrial fibrillation	11	
Bradycardia	14	
Coronary artery disease	10	
Palpitations	4	
Eye disorders	**11**	**8 (2.5%)**
Vision blurred	4	
Gastrointestinal disorders	**20**	**16 (5.1%)**
General disorders and administration site conditions	**23**	**20 (6.3%)**
Chest pain	10	
Vascular stent stenosis	4	
Infections and infestations	**61**	**43 (13.6%)**
COVID-19	9	
Cellulitis	4	
Influenza	4	
Pneumonia	6	
Urinary tract infection	9	
Injury, poisoning and procedural complications	**42**	**38 (12.0%)**
Fall	4	
Post-procedural hypotension	10	
Investigations	**11**	**10 (3.2%)**
Troponin increased	4	
Metabolism and nutrition disorders	**12**	**10 (3.2%)**
Hypokalaemia	4	
Musculoskeletal and connective tissue disorders	**22**	**16 (5.1%)**
Neck pain	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**10**	**10 (3.2%)**
Nervous system disorders	**66**	**50 (15.8%)**
Carotid artery stenosis	18	
Dizziness	5	
Headache	6	
Syncope	7	
Renal and urinary disorders	**14**	**14 (4.4%)**
Acute kidney injury	8	
Respiratory, thoracic and mediastinal disorders	**13**	**13 (4.1%)**

System Organ Class Preferred Term	Number of events	Number (%) of Subjects
Skin and subcutaneous tissue disorders	**8**	**7 (2.2%)**
Surgical and medical procedures	**7**	**7 (2.2%)**
Vascular disorders	**86**	**73 (23.1%)**
Hypertension	8	
Hypotension	43	
Peripheral artery occlusion	4	
Peripheral vascular disorder	7	

System organs with a total rate of aggregated AEs and individual AEs with <1% prevalence are not displayed.

4. Subgroup Analyses

The following baseline values were evaluated for potential association with safety and effectiveness outcomes: sex, age, race/ethnicity, and symptomatic status. The primary composite safety and effectiveness endpoint rate and its two-sided exact 95% confidence interval is presented within each of the following subgroups for the ITT population evaluable for the primary endpoint at 1-year (n = 300) in Table 19. The study was not specifically powered for these subgroups. The purpose of these subgroup analyses is to assess consistency of results across subgroups. Although numerical differences between groups can be noted, all Confidence Intervals (CIs) overlap between subgroups.

Table 19: Subgroup Analysis for Primary Endpoint (ITT)

Category / Subgroup	Primary Endpoint (%, n/N)	95% CI
Sex		
Male	2.6% (5/191)	(0.9%, 6.0%)
Female	0.9% (1/109)	(0.0%, 5.0%)
Age		
Below the median (70.0)	3.6% (5/139)	(1.2%, 8.2%)
Above the Median (70.0)	0.6% (1/161)	(0.0%, 3.4%)
Race / Ethnicity		
Caucasian	2.1% (6/292)	(0.8%, 4.4%)
Non-Caucasian	0.0% (0/8)	(0.0%, 36.9%)
Symptomatic Status		
Symptomatic	6.8% (5/74)	(2.2%, 15.1%)
Asymptomatic	0.4% (1/226)	(0.0%, 2.4%)

Post-hoc Subgroup Analyses for CGuard Prime Subgroup

The CGuard Prime Carotid Stent System was introduced in the last phase of the study and was implanted in 32 patients. The CGuard and CGuard Prime Carotid Stent Systems are the same implantable stent and only differ in their delivery system and handles. A post-hoc analysis was conducted on the primary endpoint for only those subjects who received a CGuard Prime device as shown in Table 20.

A post-hoc analysis was performed on the same group using the pre-specified definitions of technical and treatment success endpoints (i.e. final residual diameter stenosis <30%) (Table 21).

Table 20: Primary Endpoint in ITT Subjects Treated with CGuard Prime (Post-hoc analysis)

	CGuard Prime (N = 32) Proportion (n/N), 95% CI
Primary Endpoint	0.00% (0/27), (0.00%, 12.77%)
MAE through 30 Days	0.00% (0/32), (0.00%, 10.89%)
Death (all cause)	0.00% (0/32), (0.00%, 10.89%)
Stroke	0.00% (0/32), (0.00%, 10.89%)
Myocardial Infarction*	0.00% (0/32), (0.00%, 10.89%)
Ipsilateral Stroke Days 31-365	0.00% (0/27), (0.00%, 12.77%)

Table is hierarchical. Only the first occurring event that meets the definition of one of the components is presented.
*Classified based on the ARC2 definition

Table 21: Technical and Treatment Success in ITT Subjects treated with CGuard Prime vs CGuard (Post-hoc Analysis)

	CGuard Prime (N = 32) Proportion (n/N), 95% CI	CGuard (N = 284) Proportion (n/N), 95% CI
Technical Success	93.8% (30/32), (79.2%, 99.2%)	91.5% (248/271), (87.5%, 94.5%)
Treatment Success	93.8% (30/32), (79.2%, 99.2%)	90.4% (245/271), (86.3%, 93.6%)

These post-hoc subgroup analyses were not powered to detect differences between CGuard and CGuard Prime Carotid Stent Systems. 95% CIs overlap substantially and show no evidence of a difference in technical, treatment success or in the primary endpoint (or its components) between CGuard and CGuard Prime Carotid Stent Systems.

5. Pediatric Extrapolation

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

D. 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 26 investigators, none were an employee of the sponsor, and six had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 6
- Significant payment of other sorts: 4
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 4

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

XI. 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.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety and Effectiveness Conclusions

The risks of the device are based on non-clinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. Non-clinical testing performed during the design and development of the CGuard Prime Carotid Stent System confirmed the product design characteristics, specifications, and intended use. The non-clinical engineering testing conducted on the stent and delivery system demonstrated that the performance characteristics met the product specifications. The biocompatibility and *in vivo* animal testing demonstrated that the acute and chronic *in vivo* performance characteristics of the CGuard Prime Carotid Stent System provide reasonable assurance of safety and acceptability for clinical use. The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The shelf-life testing has established acceptable performance for a labeled shelf life up to 15 months.

A prospective, multicenter single arm study (C-GUARDIANS) was conducted to support approval of this device. The primary composite endpoint of the clinical study was defined as death, any stroke, or myocardial infarction (MI) through 30 days post-index procedure, or ipsilateral stroke between 31 days and 1 year. The proportion of subjects with a primary endpoint event in the ITT population was 2.00% (6/300), with one-sided 95% upper confidence limit (UCL) of 4.3%, which was significantly less than the 11.6% performance goal (p value <0.001). The Kaplan-Meier estimate for the primary endpoint was 1.93% in the ITT population and 1.71% in the PP population. The secondary endpoint of technical success was 91.7% in the ITT population. The rate of in stent restenosis, TLR and CD-TLR at 1-year were 2.5%, 1.0% and 0.3%, respectively. The observed adverse event rate is similar to other carotid stent studies and supports the safety of the device. These results indicate that the CGuard Prime

Carotid Stent System met its primary endpoint for treatment of carotid artery disease and is a durable treatment option for up to one year. There were no unanticipated adverse events in the study.

B. Benefit-Risk Determination

The probable benefits of the device are based on data collected in the C-GUARDIANS clinical study conducted to support PMA approval as described above. The C-GUARDIANS trial has established the safety and effectiveness of the CGuard Prime Carotid Stent System, and the results are in alignment with other approved carotid stents.

In conclusion, given the available information, the data support that for the treatment of carotid artery stenosis in patients deemed at high surgical risk for carotid endarterectomy, the overall benefits of using the CGuard Prime Carotid Stent System outweigh the overall risks.

1. Patient Perspective

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

C. Overall Conclusions

The clinical and non-clinical data in this application support a reasonable assurance that the device is safe and effective when used in accordance with the indications for use. The clinical study met the pre-specified primary endpoint. Therefore, it is reasonable to conclude that the benefits of 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).

XIII. CDRH DECISION

CDRH issued an approval order on June 23, 2025. The final conditions of approval cited in the approval order are described below.

Post-Approval Study – Continued Follow-up Study. This study should be conducted per protocol PRO-9017 Version F (dated March 21, 2023). This study is a prospective, multicenter follow-up of the pivotal study (G190185) that treated 316 subjects from 24 investigational sites. It will evaluate the long-term safety and effectiveness of the CGuard Prime Carotid Stent System. All 303 remaining subjects active at the end of the 12-month evaluation will continue to be followed annually through 36 months. Follow-up at the 24- and 36-month timepoints will include the following: Anticoagulant and/or antiplatelet medications (concomitant medications), targeted physical exam, NIH Stroke Scale, modified Rankin Scale, carotid duplex ultrasound, INR for subjects on long term VKA anticoagulant therapy, and Adverse Event Assessment.

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

XIV. 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.