SECTION 4.0
SPONSOR EXECUTIVE SUMMARY

4.1 History of Carotid Artery Disease Treatment Options

Treatment options for carotid artery disease include best medical therapy, carotid endarterectomy (CEA) and carotid artery stenting (CAS). Each of the three options plays a unique role in the prevention of stroke. Medical therapy as a non-invasive approach has its advantage, as it does not require a surgical procedure or hospitalization. To date, aspirin monotherapy is still the best medical therapy because it requires a low dose, is less expensive, and is relatively safe. However, the role of medical therapy in stroke prevention is limited, with an average of 15-18% relative risk reduction (RRR) for aspirin [The SALT Collaborative Group, 1991] [The Dutch TIA Trial Study Group, 1991] [Farrell et al, 1991] [Eikelboom et al, 2002]. Some antiplatelet combination therapies show enhanced efficacy (20-37% RRR) but also displays increased serious adverse events [Hass et al, 1989] [ESPS Group, 1990] [Diener et al, 1996] [Halkes et al, 2006]. Furthermore, medical therapies such as antiplatelet, lipid control, and angiotensin-related hypertension control agents, have become general medical practice in the patient population who has related risk factors.

Clinical trials have evaluated the outcome of CEA as compared to medical therapy. The ACAS [Executive Committee for ACAS, 1995] and ACST [Halliday et al, 2004] trials have demonstrated that CEA plus best medical therapy has a 53% and a 60% RRR over best medical therapy, respectively. CEA has been proven effective in reducing the risk of stroke and is now considered the gold standard of care for patient populations with carotid stenosis. Unless other risk factors warrant caution, subjects with carotid stenosis are currently recommended for CEA under AHA guidelines.

CAS is another treatment option for patients. CAS has been studied since the 1990s in the high surgical risk patient population [Yadav, Wholey et al, 2004] and has demonstrated consistently acceptable clinical outcomes in the high surgical risk population. In 2004, the Abbott Vascular RX Acculink Carotid Stent System was approved for use in patients at high risk for adverse events from CEA. Clinical outcomes in a standard surgical risk population have been studied in the CREST trial. The results of the CREST trial demonstrate that the safety profile of CAS is comparable to CEA in standard surgical risk patients; these data form the basis of this PMA Supplement to expand the indication of the Abbott Vascular RX Acculink Carotid Stent System.

4.2 The RX Acculink Carotid Stent System

The RX Acculink Carotid Stent System was approved in the US for use in high surgical risk subjects on August 30, 2004. The device is commercially available in over 90 countries. As of November 2010, over 128,000 RX Acculink Carotid Stent Systems have been distributed world-wide.

The RX Acculink Carotid Stent System is comprised of the nickel-titanium self-expanding Acculink Carotid Stent and the rapid-exchange (RX) Acculink Stent Delivery System. The RX
Acculink Carotid Stent System is a single-use device that uses a sheath to mechanically constrain the stent at a small diameter for delivery to the treatment site.

The RX Acculink Carotid Stent System is currently indicated for the treatment of patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet specified criteria outlined in the product labeling.

There are no changes to the Acculink stent, implant technique or anatomical location for the expanded indication.

### 4.3 Proposed Indications for Use

#### High Surgical Risk

The RX Acculink Carotid Stent System, used in conjunction with Abbott Vascular’s Accunet or Emboshield family of Embolic Protection Systems (EPS), is indicated for the treatment of patients at high risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the criteria outlined below:

1. Patients with neurological symptoms and \( \geq 50\% \) stenosis of the common or internal carotid artery by ultrasound or angiogram OR patients without neurological symptoms and \( \geq 80\% \) stenosis of the common or internal carotid artery by ultrasound or angiogram, AND
2. Patients must have a reference vessel diameter within the range of 4.0 mm and 9.0 mm at the target lesion.

#### Standard Surgical Risk

The RX Acculink Carotid Stent System, used in conjunction with the Accunet Embolic Protection System (EPS), is indicated for the treatment of patients at standard risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the criteria outlined below:

1. Patients with neurological symptoms and \( \geq 50\% \) stenosis of the common or internal carotid artery OR patients without neurological symptoms \( \geq 70\% \) stenosis of the common or internal carotid artery, AND
2. Patients must have a reference vessel diameter within the range of 4.0 mm and 9.0 mm at the target lesion.

### 4.4 CREST (Carotid Revascularization Endarterectomy vs. Stenting Trial)

CREST was created in collaboration with the U.S. National Institute of Neurological Disorders of the National Institute of Health (NIH) and the University of Medicine and Dentistry of New Jersey (UMDNJ) and funded by Abbott Vascular. The CREST Investigational Device Exemption (IDE) application was conditionally approved in April of 2000. CREST is the first randomized trial comparing CAS and CEA in standard surgical risk population. CREST was designed to study the use of carotid stents for treating disease in extracranial internal carotid arteries due to atherosclerosis in the standard surgical risk population. CREST was a
prospective, randomized (1 CAS: 1 CEA), parallel, two-arm, multi-center trial with blinded endpoint evaluation. A Lead-In Phase was designed to allow for clinical center start-up and physician credentialing as many interventionalists participating in the trial were inexperienced in carotid stenting, an emerging therapy at that time. CREST was initially approved to enroll up to 20 lead-in subjects per enrolling interventionalist and up to 2500 subjects in the randomized phase.

The primary safety and effectiveness endpoint of CREST was the composite of death, stroke and myocardial infarction (DSMI) at 30 days plus stroke ipsilateral to the study artery between 31 and 365 days. These endpoint events have historically been used to assess the safety and effectiveness of carotid stenting in symptomatic and asymptomatic patient populations. Key additional analyses included peri-procedural DSMI at 30 days, target lesion revascularization (TLR) at 12 months, access site complications, cranial nerve injury and the composite endpoint of DSMI at 30 days plus stroke ipsilateral to study artery after 31 days.

4.5 CREST Results in the Per Protocol Population (Primary Analysis)

The results from CREST support an expanded indication for the Acculink System for standard risk subjects with carotid artery disease.

- CREST has met the primary endpoint of the trial with $p < 0.05$.
- In the primary analysis of the one-year composite primary endpoint, the event rate of DSMI during the 30-day peri-procedural period plus ipsilateral stroke between 31 and 365 days is 7.1% in the CAS arm and 6.6% in the CEA arm.
- The observed difference between the primary endpoint event rates for CAS and CEA arms is 0.5% with a 95% upper confidence limit of 2.26% within the pre-specified non-inferiority margin of 2.6% ($p = 0.0245$).

The additional analyses also demonstrated:

- Both symptomatic and asymptomatic subgroups met the endpoint with $p < 0.05$ in the pre-specified non-inferiority test.
- Within the non-octogenarian subgroup, the composite endpoint rates are 6.7% in the CAS arm vs. 6.2% in the CEA arm. The analysis reaches statistical significance with a $p$-value $< 0.05$ with a non-inferiority margin of 2.6%.
- The observed difference between the 30-Day DSMI event rates of 5.8% for CAS and 5.1% for CEA is 0.6% with a 95% upper confidence limit of 2.2% within the pre-specified non-inferiority margin of 2.3% ($p = 0.0401$). Therefore, CREST has met the DSMI endpoint of the trial with $p < 0.05$.
- There were statistically significantly fewer access site complications in the CAS arm (1.1%) than the CEA arm (3.5%).
- For the subjects in whom CEA was attempted, the data show that 5.2% of subjects had cranial nerve injury which remained unresolved in 3.5% of subjects at 1 month and in 2.0% of subjects at 6 months post-procedure. No subjects who received CAS reported cranial nerve injury.
- The freedom from clinically-driven TLR at 12 months by Kaplan-Meier Survival Analysis is 98.8% in the CAS arm and 99.0% in the CEA arm.
• The 4-year long-term composite endpoint event rates, DSMI plus ipsilateral stroke between 31 days and 4 years, are 8.8% in the CAS arm and 8.2% in the CEA arm with a hazard ratio (HR) of 1.08.

4.6 CREST Results in Other Analysis Populations

The primary endpoint was also met in all other analysis groups, e.g. the Per-Protocol (Adjusted) and Intent-to-Treat populations.

4.7 Conclusions

All the CREST endpoints were met supporting the proposed indication, demonstrating that CAS is statistically non-inferior to CEA when performed using the Acculink Carotid Stent System to treat standard surgical risk subjects with disease in the internal carotid artery. The data from CREST revealed a low event rate for both CAS and CEA and establish an acceptable benefit risk profile. Both long term and short term outcomes of CREST have established a reasonable assurance of safety and effectiveness of the Acculink Carotid Stent System.