**Absorb GT1™**
**Bioresorbable Vascular Scaffold (BVS) System**
**Instructions for Use**

Rx ONLY

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## 1.0 DEVICE DESCRIPTION

The Absorb GT1 Bioresorbable Vascular Scaffold (BVS) System is a temporary coronary scaffold comprised of a fully bioresorbable scaffold and bioresorbable polymer coating. Absorb™ improves symptoms in patients with evidence of ischemic heart disease and is naturally resorbed by the body in two to three years.

The Absorb GT1 BVS System includes:

- A pre-mounted polymer poly (L-lactide) (PLLA) scaffold coated with a blend of the antiproliferative drug everolimus and polymer poly (D,L-lactide) (PDLLA) in a 1:1 ratio. The available dose of everolimus on the scaffold is shown in **Table 1.0-1**.

**Table 1.0-1: Drug Content in Absorb GT1 BVS**

| Scaffold Diameter (mm) | Scaffold Length (mm) | Drug Dose (μg) |
|---|---|---|
| 2.5, 3.0 | 8 | 76 |
| 2.5, 3.0 | 12 | 114 |
| 2.5, 3.0 | 18 | 181 |
| 2.5, 3.0 | 23 | 228 |
| 2.5, 3.0 | 28 | 276 |
| 3.5 | 12 | 135 |
| 3.5 | 18 | 197 |
| 3.5 | 23 | 246 |
| 3.5 | 28 | 308 |

- Four radiopaque markers located at the end rings of the scaffold mark the scaffold length prior to deployment and after expansion in the artery because the Absorb GT1 Bioresorbable Vascular Scaffold itself is not visible under fluoroscopy.

- Two radiopaque markers, located underneath the balloon, fluoroscopically mark the working length of the balloon and the location of the undeployed scaffold of the scaffold delivery system.

- Absorb GT1 BVS System has a rapid exchange (RX) scaffold delivery system.

- Two proximal delivery system shaft markers (95 cm and 105 cm proximal to the distal tip) indicate the relative position of the delivery system to the end of brachial or femoral guiding catheter. Working catheter length is 145 cm.

- A shaft color change denotes the guide wire exit notch.

**Note:** The Absorb GT1 BVS System utilizes the identical scaffold as the previous generation Absorb BVS System. Within this document, the scaffold for both systems is referred to synonymously as the “Absorb GT1 BVS,” the “Absorb scaffold,” or “Absorb.”

**Table 1.0-2: *In Vitro* Device Specifications**

| Scaffold Diameter (mm) | Scaffold Length (mm) | * Minimum Guiding Catheter Compatibility (ID) | ** *In Vitro* Scaffold Nominal Pressure | | Rated Burst Pressure – RBP | | Scaffold Free Area (%) |
|---|---|---|---|---|---|---|---|
| | | | atm | kPa | atm | kPa | |
| 2.5 | 8 | 6F (0.070”/1.8 mm) | 6 | 608 | 16 | 1621 | 68 |
| 2.5 | 12 | 6F (0.070”/1.8 mm) | 6 | 608 | 16 | 1621 | 68 |
| 2.5 | 18 | 6F (0.070”/1.8 mm) | 6 | 608 | 16 | 1621 | 68 |
| 2.5 | 23 | 6F (0.070”/1.8 mm) | 6 | 608 | 16 | 1621 | 68 |
| 2.5 | 28 | 6F (0.070”/1.8 mm) | 6 | 608 | 16 | 1621 | 68 |
| 3.0 | 8 | 6F (0.070”/1.8 mm) | 7 | 709 | 16 | 1621 | 72 |
| 3.0 | 12 | 6F (0.070”/1.8 mm) | 7 | 709 | 16 | 1621 | 73 |
| 3.0 | 18 | 6F (0.070”/1.8 mm) | 7 | 709 | 16 | 1621 | 73 |
| 3.0 | 23 | 6F (0.070”/1.8 mm) | 7 | 709 | 16 | 1621 | 73 |
| 3.0 | 28 | 6F (0.070”/1.8 mm) | 7 | 709 | 16 | 1621 | 73 |
| 3.5 | 12 | 6F (0.070”/1.8 mm) | 6 | 608 | 16 | 1621 | 73 |
| 3.5 | 18 | 6F (0.070”/1.8 mm) | 6 | 608 | 16 | 1621 | 73 |
| 3.5 | 23 | 6F (0.070”/1.8 mm) | 6 | 608 | 16 | 1621 | 73 |
| 3.5 | 28 | 6F (0.070”/1.8 mm) | 6 | 608 | 16 | 1621 | 74 |

* See individual manufacturer specifications for (F) equivalent.

** Ensure full deployment of the scaffold (see **Section 12.6 - Clinician Use Information, Deployment Procedure**).

**Note:** Deployment pressures should be based on lesion characteristics.

- A non-sterile temperature monitor for the shipping and storage of the Absorb GT1 BVS System has been included with the product. Before use of this product, check the temperature indicator located through the window in the back of the product box. Consult product carton or carton insert for indicator legend.

## 2.0 INDICATIONS

The Absorb GT1 Bioresorbable Vascular Scaffold (BVS) is a temporary scaffold that will fully resorb over time and is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* native coronary artery lesions (length ≤ 24 mm) with a reference vessel diameter of ≥ 2.5 mm and ≤ 3.75 mm.

## 3.0 CONTRAINDICATIONS

The Absorb GT1 BVS System is contraindicated for use in:

- Patients who cannot tolerate, including allergy or hypersensitivity to, procedural anticoagulation or post-procedural antiplatelet regimen.

- Patients with a known allergy or hypersensitivity to everolimus or structurally related compounds, device materials (poly [L-lactide], poly [D,L-lactide], platinum), or contrast medium who cannot be adequately premedicated.

## 4.0 WARNINGS

- **For single use only.** Do not resterilize or reuse. Note the product "Use by" date on the package.
- Careful selection of the target lesion reference vessel diameter to the scaffold diameter is required to minimize potential damage to the scaffold during post-dilatation and ensure adequate scaffold apposition and appropriate minimum lumen diameter.
- Adequate lesion preparation prior to scaffold implantation is required to ensure safe delivery of the scaffold across the target lesion. It is not recommended to treat patients having a lesion that prevents complete inflation of an angioplasty balloon. It is strongly recommended to achieve a residual stenosis between 20% and 40% after pre-dilatation to enable successful delivery and full expansion of the scaffold.
- Ensure the scaffold is not post-dilated beyond the allowable expansion limits (see **Section 12.7 - Clinician Use Information, Further Expansion of the Deployed Scaffold**).
- Antiplatelet therapy should be administered post-procedure (see **Section 9.1 Individualization of Treatment**).
- This product should not be used in patients who are not likely to comply with the recommended antiplatelet therapy.
- Judicious selection of patients is necessary, since the use of this device carries the associated risk of scaffold thrombosis, vascular complications, and / or bleeding events.
- If quantitative imaging determines a vessel size < 2.5 mm, do not implant the Absorb GT1 BVS. Implantation of the device in vessels < 2.5 mm may lead to an increased risk of adverse events such as myocardial infarction and scaffold thrombosis.

## 5.0 PRECAUTIONS

### 5.1 Scaffold Handling

- Implantation of the scaffold should be performed **only** by physicians who have received appropriate training.
- Scaffold placement should only be performed at centers where emergency coronary artery bypass graft surgery (CABG) is available.
- Ensure that the inner package sterile barrier has not been opened or damaged prior to use.
- Care should be taken to control the guiding catheter tip during scaffold delivery, deployment, and balloon withdrawal. Before withdrawing the scaffold delivery system, visually confirm complete balloon deflation by fluoroscopy to avoid guiding catheter movement into the vessel and subsequent arterial damage.

- Special care must be taken not to handle or in any way disrupt the scaffold from the balloon. This is most important during catheter removal from packaging, placement over the guide wire, and advancement through the rotating hemostatic valve adapter and guiding catheter hub.

- **Do not manipulate, touch, or handle the scaffold** with your fingers, as this may cause coating damage, contamination, or dislodgement of the scaffold from the delivery balloon.

- Use only the appropriate balloon inflation media. Do not use air or any gaseous medium to inflate the balloon, as this may cause uneven expansion and difficulty in deployment of the scaffold.

## 5.2 Scaffold Placement

- Devices (i.e., guide sheaths) that decrease the inner diameter of the guide catheter outside of the Absorb GT1 BVS minimum guide catheter compatibility (**Table 1.0-2**) must not be used with the Absorb GT1 BVS System. Do not insert a 5-in-6, or a 6-in-7 guide sheath into a 6F or 7F guiding catheter, as doing so will result in an inner diameter that is too small for use with the Absorb GT1 BVS System.

- **Do not prepare or preinflate the delivery system prior to scaffold deployment**, other than as directed. Use balloon purging technique described in **Section 12.4.4 - Clinician Use Information, Preparation, Delivery System Preparation**.

- Pre-dilatation should be performed with an angioplasty balloon. Cutting or scoring balloons can be used per physician discretion, if the lesion appears to be mildly calcified.

- When introducing the delivery system into the vessel, do not induce negative pressure on the delivery system. This may cause dislodgement of the scaffold from the balloon.

- Do not torque the catheter more than one (1) full turn.

- Use caution when advancing the Absorb GT1 BVS across the lesion. Multiple attempts to cross a lesion may lead to scaffold damage or dislodgement.

- Implanting a scaffold may lead to dissection of the vessel distal and / or proximal to the scaffold and may cause abrupt closure / total occlusion of the vessel, requiring additional intervention (CABG, further dilatation, placement of additional scaffolds, or other).

- In the rare event of abrupt closure / total occlusion following scaffold placement, a bailout implant may be inserted and deployed within the scaffold such that the Absorb GT1 BVS is completely covered by the bailout implant. All abrupt closures must be treated as an emergency per the hospital standard of care.

  **Note:** It is recommended that bailouts for abrupt closure / total occlusion be done with a metallic everolimus-eluting stent of appropriate size.

- An unexpanded scaffold may be retracted into the guiding catheter **one time only**. An unexpanded scaffold should not be reintroduced into the artery once it has been pulled back into the guiding catheter. Subsequent movement in and out through the distal end

of the guiding catheter should not be performed, as the scaffold may be damaged or dislodged during retraction back into the guiding catheter.

- Should resistance be felt at any time during removal of the undeployed Absorb GT1 BVS System, please refer to the steps provided in **Section 5.4 - Precautions, Scaffold / System Removal**.

- Do not expand the scaffold if it is not properly positioned in the vessel (see **Section 5.4 - Precautions, Scaffold / System Removal**).

- The inflated balloon diameter of the system used to deploy the scaffold should approximate the diameter of the vessel. To ensure full expansion of the scaffold, the balloon should be inflated to a minimum of nominal pressure.

- **Do not exceed the Rated Burst Pressure (RBP) as indicated on the product label.** Monitor balloon pressures during inflation. Use of pressures higher than specified on the product label may result in a ruptured balloon, with possible intimal damage and dissection.

- Post-dilatation is strongly recommended for optimal scaffold apposition. When performed, post-dilatation should be at high pressure (> 16 atm) with a noncompliant balloon.

- Under-expansion of the scaffold may result in scaffold movement. Care must be taken to properly size the scaffold to ensure that the scaffold is in full contact with the arterial wall upon deflation of the balloon. All efforts should be made to assure that the scaffold is not under dilated. Refer to **Section 12.7 Clinician Use Information – Further Expansion of the Deployed Scaffold**

- In small vessels (visually assessed as ≤ 2.75 mm), on-line QCA or intravascular imaging is strongly recommended to accurately measure and confirm appropriate vessel sizing (≥ 2.5 mm).

- Balloon dilatation of any cells of a deployed Absorb GT1 BVS may cause scaffold damage. **Avoid scaffolding across any side branches ≥ 2.0 mm in diameter.** Placement of a scaffold has the potential to compromise side branch patency.

- Scaffold retrieval methods (use of additional wires, snares, and / or forceps) may result in additional trauma to the coronary vasculature and / or the vascular access site. Complications may include bleeding, hematoma, or pseudoaneurysm.

- When treating multiple lesions within the same vessel, scaffold / stent the distal lesion prior to scaffolding the proximal lesion. Scaffolding / stenting in this order obviates the need to cross the proximal scaffold in placement of the distal scaffold / stent, and reduces the chance of damaging or dislodging the proximal scaffold / stent.

- When multiple Absorb GT1 BVS or drug-eluting stents are required, only Absorb GT1 BVS or everolimus-eluting scaffolds / stents must be used. Potential interaction with other drug-eluting or coated scaffolds / stents has not been evaluated and should be avoided.

- The extent of the patient's exposure to drug and polymer is directly related to the number of scaffolds implanted. The safety of everolimus, polymer, and polymer

breakdown products was evaluated in pre-clinical studies and biocompatibility assessment of the Absorb scaffold through its life-cycle. No everolimus, polymer, or polymer breakdown product-related safety issues were identified in dosing up to the equivalent of 94 mm of Absorb scaffolding.

- It is not recommended to treat patients having a lesion with excessive tortuosity proximal to or within the lesion.

- The safety and effectiveness of the Absorb GT1 BVS in patients with prior brachytherapy of the target lesion or the use of brachytherapy for treated site restenosis in an Absorb GT1 BVS have not been established. Both vascular brachytherapy and the Absorb GT1 BVS alter arterial remodeling. The combination between those two treatments has not been established.

### 5.3 Use in Conjunction with Other Procedures

- While vessel preparation in complex lesions may include the use of various mechanical atherectomy devices, the safety and effectiveness have not been formally established in clinical trials with use of either mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters in conjunction with Absorb GT1 BVS implantation.

### 5.4 Scaffold / System Removal

- Scaffold delivery system removal prior to scaffold deployment:

  If removal of a scaffold system is required prior to deployment, ensure that the guide catheter is coaxially positioned relative to the scaffold delivery system and cautiously withdraw the scaffold delivery system into the guiding catheter. Should **unusual resistance** be felt **at any time** when withdrawing the scaffold into the guide catheter, the scaffold delivery system and the guide catheter should be **removed as a single unit**. This should be done under direct visualization with fluoroscopy.

- Withdrawal of the scaffold delivery system / post-dilatation balloon from the deployed scaffold:

  1. Deflate the balloon by pulling negative on the inflation device. Larger and longer balloons will take more time (up to 30 seconds) to deflate than smaller and shorter balloons. Confirm balloon deflation under fluoroscopy.
  2. Position the inflation device to “negative” or “neutral” pressure.
  3. Stabilize guide catheter position just outside coronary ostium and anchor in place. Maintain guide wire placement across scaffold segment.
  4. Gently remove the scaffold delivery system / post-dilatation balloon with slow and steady pressure.
  5. Tighten the rotating hemostatic valve.

  **Notes:**

  1. **If, during withdrawal of the catheter from the deployed scaffold, resistance is encountered, use the following steps to improve balloon rewrap:**

- Re-inflate the balloon up to nominal pressure, deflate and change pressure to neutral.
- Repeat steps 1 through 5 above.

2. After successful withdrawal of the balloon from the deployed scaffold, should **any resistance** be felt **at any time** when withdrawing the scaffold delivery system or post-dilatation balloon into the guide catheter, **remove the entire system as a single unit**.

- Failure to follow the steps and / or applying excessive force to the delivery system can potentially result in loss of or damage to the scaffold and / or delivery system components.

- If it is necessary to retain guide wire position for subsequent artery / lesion access, leave the guide wire in place and remove all other system components.

## 5.5 Post Implant

- **If necessary to cross a newly deployed scaffold** with a guide wire, balloon, delivery system, or imaging catheters, exercise care to avoid disrupting the scaffold geometry.

- Subsequent restenosis may require repeat dilatation of the arterial segment containing the scaffold. The long-term outcome following repeat dilatation of endothelialized scaffolds is unknown at present.

## 5.6 Use in Special Populations

### *5.6.1 Pregnancy*

Pregnancy Category C: see **Section 6.5 - Drug Information, Pregnancy**. The Absorb GT1 BVS has not been tested in pregnant women or in men intending to father children. Effects on the developing fetus have not been studied. Effects of a similar stent, XIENCE V, on prenatal and postnatal rat development were no different than the controls. When administered at oral doses of 0.1 mg/kg or above to animals, everolimus has shown reproductive toxicity effects including embryo toxicity and foetotoxicity.[1]

Effective contraception should be recommended to be initiated before implanting Absorb GT1 BVS and continued for one year after implantation. While there is no contraindication, the risks and reproductive effects are unknown at this time.

### *5.6.2 Lactation*

See **Section 6.6 - Drug Information, Lactation**. A decision should be made whether to discontinue nursing prior to scaffold implantation, considering the importance of the scaffold to the mother.

[1] Certican® UK label Mar 2015, Afinitor® EU authorization SPC Dec 2014, Votubia® EU SPC Sept 2014, Afinitor® US label Jan 2015, and Zortress® US label Sept 2015. Refer to www.MHRA.gov.uk, www.ema.europa.eu, and www.fda.gov for the most recent versions of these SPC/labels.

### *5.6.3 Gender*

The assessment of gender effect in the ABSORB III trial for the primary endpoint of target lesion failure (TLF) at 1 year showed no difference in treatment between Absorb and XIENCE, with an interaction p-value between female and male subgroups of 0.6763. Within each subgroup, there were no statistical differences in 1-year TLF between Absorb and XIENCE.

### *5.6.4 Ethnicity*

The assessment of ethnicity effect in the ABSORB III trial for the primary endpoint of TLF at 1 year showed no differences in treatment between Absorb and XIENCE, with an interaction p-value between white and non-white subgroups of 0.9835. Within each subgroup, there were no statistical differences in 1-year TLF between Absorb and XIENCE.

### *5.6.5 Pediatric Use*

The safety and effectiveness of Absorb GT1 BVS in pediatric subjects have not been established.

### *5.6.6 Geriatric Use*

The ABSORB III trial had a median subject age of 64 years, with no upper age limit. The assessment of geriatric effect in the ABSORB III trial for the primary endpoint of TLF at 1 year showed no differences in treatment between Absorb and XIENCE, with an interaction p-value between age ≥ median and age < median subgroups of 0.6924. Within each subgroup, there were no statistical differences in 1-year TLF between Absorb and XIENCE.

## 5.7 MRI (Magnetic Resonance Imaging) Safety Information

Non-clinical testing has demonstrated the Absorb GT1 BVS is MR Conditional. A patient with this device can be safely scanned in all MR environments 3T or less.

## 5.8 Drug Interactions

See **Section 6.3 - Drug Information, Interactions with Drugs or Other Substances**. Several drugs are known to affect everolimus metabolism, and other drug interactions may also occur. Everolimus is known to be a substrate for both cytochrome P4503A4 (CYP3A4) and P-glycoprotein (PgP). Everolimus absorption and subsequent elimination may be influenced by drugs that affect these pathways. Everolimus has also been shown to reduce the clearance of some prescription medications when administered orally along with cyclosporine (CsA). Formal drug interaction studies have not been performed with the Absorb GT1 BVS because of limited systemic exposure to everolimus eluted from Absorb GT1 BVS (see **Section 6.2 - Drug Information, Pharmacokinetics**). Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall, when deciding to place the Absorb GT1 BVS in a patient taking a drug with known interaction with everolimus, or when deciding to initiate therapy with such a drug in a patient who has recently received Absorb GT1 BVS.

### 5.9 Immune Suppression Potential

Everolimus, the Absorb GT1 BVS active ingredient, is an immunosuppressive agent. Immune suppression was not observed in the ABSORB family of clinical trials. However, for patients who receive several Absorb GT1 BVS simultaneously, it may be possible for everolimus systemic concentrations to approach immunosuppressive levels temporarily, especially in patients who also have hepatic insufficiency or who are taking drugs that inhibit CYP3A4 or P-glycoprotein. Therefore, consideration should be given to patients taking other immunosuppressive agents or who are at risk for immune suppression.

### 5.10 Lipid Elevation Potential

Oral everolimus use in renal transplant and advanced renal cell carcinoma patients was associated with increased serum cholesterol and triglycerides, which in some cases required treatment. The effect was seen with both low and high dose prolonged oral therapy in a dose related manner. When used according to the indications for use, exposure to systemic everolimus concentrations from the Absorb GT1 BVS is expected to be significantly lower than concentration exposure usually obtained in transplant patients. Increased serum cholesterol and triglycerides were not observed in the ABSORB family of clinical trials.

Oral administration of everolimus in combination with cyclosporine has been associated with increased serum cholesterol and triglycerides. Therefore, patients treated with cyclosporine should be monitored for changes in lipid profiles.

## 6.0 DRUG INFORMATION

### 6.1 Mechanism of Action

The mechanism by which the Absorb GT1 BVS inhibits neointimal growth as seen in pre-clinical and clinical studies has not been established. At the cellular level, everolimus inhibits growth factor-stimulated cell proliferation. At the molecular level, everolimus forms a complex with the cytoplasmic protein FKBP-12 (FK 506 Binding Protein). This complex binds to and interferes with FKBP-12 Rapamycin Associated Protein (FRAP), also known as mammalian target of rapamycin (mTOR), leading to inhibition of cell metabolism, growth, and proliferation by arresting the cell cycle at the late G1 stage.

### 6.2 Pharmacokinetics

Everolimus elution from the Absorb scaffold post-implantation has been evaluated in a pharmacokinetic (PK) sub-study, which is part of the ABSORB III clinical trial design studying the Absorb scaffold in the United States (US). A total of 12 subjects who received only Absorb scaffolds at two investigational sites in the US were registered in the PK sub-study. All subjects had single target lesions that were treated with only Absorb. The number of scaffolds implanted per subject was one or two. The total dose of everolimus received by the subjects ranged from 181 to 443 µg. **Table 6.2-1** provides whole blood everolimus PK parameters determined from the subjects receiving Absorb.

**Table 6.2-1: Pharmacokinetic Results of Everolimus after Implantation of at Least One Absorb (Individual Dose Ranged from 181 μg - 443 μg)**

| Pharmacokinetics of everolimus | ABSORB III PK Sub-Study |
|---|---|
| N | 12 |
| Stents/Scaffolds used | 1 - 2 |
| Dose (μg) | 181 - 443 |
| $C_{max}$ (ng/mL) | 1.085 - 4.460 |
| $AUC_{last}$ (ng*h/mL) | 25.37 - 104.6 |
| $T_{max}$ (h) | 0.17 - 2.37 |
| $t_{1/2}$ (h) | 45.9 - 115 |

Note: Ranges are provided for dose, $C_{max}$, $AUC_{last}$, $T_{max}$, and $t_{1/2}$

Everolimus blood concentrations were low but could be quantified up to 168 hours after implantation of the last Absorb scaffold. Although short-lived, individual $C_{max}$ values (1.085 to 4.460 ng/mL) were slightly higher than the minimum systemic, chronically maintained therapeutic level of ≥ 3.0 ng/mL necessary to be effective for prevention of organ rejection. Blood concentrations were below 3.0 ng/mL in all subjects by 4 hours after the last scaffold deployment. The rapid disappearance of everolimus after implantation of the Absorb scaffold further limits the systemic extent of exposure. Therefore, everolimus blood concentrations seen with the Absorb scaffold are considered safe.

The pharmacokinetic profile for everolimus eluted from the Absorb scaffold has adequately been characterized and is consistent with previous clinical and nonclinical data. The PK characteristics of everolimus after deployment of the Absorb scaffold (dose range: 181 to 443 μg) were shown to be predictable due to dose-proportional behavior. The local arterial delivery and limited systemic exposure provide the opportunity for successful treatment of coronary lesions with limited risk associated with systemic exposure. The pharmacokinetic profiles seen with the Absorb scaffold are considered to be safe.

## 6.3 Interactions with Drugs or Other Substances

Everolimus is extensively metabolized by the cytochrome P4503A4 (CYP3A4) in the gut wall and liver, and is a substrate for the countertransporter P-glycoprotein. Everolimus has also been shown to reduce the clearance of some prescription medications when it was administered orally along with cyclosporine (CsA). Hence, everolimus, when prescribed as an oral medication, may interact with other medications that include (but are not restricted to) inhibitors and inducers of CYP3A4 isozymes; absorption and subsequent elimination of everolimus may be influenced by drugs that affect these pathways. Formal drug interaction studies have not been performed with the Absorb GT1 BVS System. Therefore, due consideration should be given to the potential for both systemic and local drug interactions in the vessel wall, when deciding to place the Absorb GT1 BVS in a subject taking a drug with known interaction with everolimus.

Everolimus, when prescribed as an oral medication, may interact with some drugs or foods including, but not limited to:

- CYP3A4 / PgP inhibitors that may increase everolimus blood concentrations:
    - Immunosuppressant cyclosporine
    - Antifungal agents (e.g., fluconazole, ketoconazole, itraconazole ketoconazole)

- Macrolide antibiotics (e.g., clarithromycin, erythromycin)
- Calcium channel blockers (e.g., verapamil, nicardipine, diltiazem)
- Protease inhibitors (e.g., nelfinavir, indinavir, amprenavir)
- Other substances (e.g., cisapride, metoclopramide, bromocriptine, cimetidine, danazol)

- CYP3A4 inducers that may decrease everolimus drug concentrations:

  - Antibiotics (e.g., rifampin, rifabutin)
  - Anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin)
  - Non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, nevirapine**)**
  - Glucocorticoids (e.g., dexamethasone, prednisone, prednisolone)
  - HMGCoA reductase inhibitors (e.g., simvastatin, lovastatin)
  - Other (e.g., St. John's Wort)

For more detailed drug interaction information, please reference the most recent everolimus drug label. [2]

### 6.4 Carcinogenicity, Genotoxicity, and Reproductive Toxicity

The carcinogenicity and reproductive toxicity of the Absorb GT1 BVS have not been evaluated; however, long-term carcinogenicity and teratology studies were performed with XIENCE V®, a similar everolimus-eluting coronary stent system. The test results from the XIENCE V stent, as described below, are applicable to the Absorb GT1 BVS. Additionally, there is no carcinogenicity and reproductive toxicity in PLA based on historical use of PLA materials in various implant applications.

A 26-week carcinogenicity study was conducted to evaluate the carcinogenic potential of XIENCE V stents following subcutaneous implantation in transgenic mice. During the course of the study, there were no abnormal clinical observations that suggested a carcinogenic effect of the test group (XIENCE V stent). The test group did not demonstrate an increased incidence of neoplastic lesions when compared to the negative control group. However, the positive control and the experimental positive control groups demonstrated notable increases in the incidence of neoplastic lesions compared to either the test or the negative control group. Based on the results of this study, the XIENCE V stent does not appear to be carcinogenic when implanted in transgenic mice for 26 weeks.

In addition, a reproductive toxicity (teratology) study was conducted in female Sprague-Dawley rats. The XIENCE V stent did not affect the fertility or reproductive capability of female Sprague-Dawley rats. There was no statistical difference between the test article (XIENCE V stent) and the control system in terms of any of the evaluated parameters. The test article had no effect on litter size and caused no increase of *in utero* mortality. Additionally, the XIENCE V stent did not cause any reproductive toxicity in the offspring in this study.

Genotoxicity studies were conducted on the Absorb scaffold *in vitro* on bacteria and mammalian cells and *in vivo*. These studies included gene mutations in bacteria (Ames Test), chromosomal damage including chromosomal aberration test and clastogenicity (chromosomal breakage) test

[2] Certican® UK label Mar 2015, Afinitor® EU authorization SPC Dec 2014, Votubia® EU SPC Sept 2014, Afinitor® US label Jan 2015, and Zortress® US label Sept 2015. Refer to www.MHRA.gov.uk, www.ema.europa.eu, and www.fda.gov for the most recent versions of these SPC/labels.

in mammalian cells, and erythrocyte micronucleus test in rodents. Based on the results of these studies, the Absorb scaffold is not genotoxic.

### 6.5 Pregnancy

Pregnancy Category C: There are no adequate everolimus or Absorb GT1 BVS-related studies in pregnant women. Effects of a similar stent, XIENCE V, on prenatal and postnatal rat development were no different than the controls (see **Section 6.4 - Drug Information, Carcinogenicity, Genotoxicity, and Reproductive Toxicity**). When administered at oral doses of 0.1 mg/kg or above to animals, everolimus has shown reproductive toxicity effects including embryotoxicity and foetotoxicity.[3] Effective contraception should be recommended to be initiated before implanting Absorb GT1 BVS and continued for one year post-implantation. The Absorb GT1 BVS should be used in pregnant women only if potential benefits outweigh potential risks.

The safety of the Absorb GT1 BVS has not been evaluated in males intending to father children.

### 6.6 Lactation

It is unknown whether everolimus is distributed in human milk. Also, everolimus pharmacokinetic and safety profiles have not been determined in infants. Consequently, mothers should be advised of potential serious adverse reactions to everolimus in nursing infants. Prior to Absorb GT1 BVS implantation, decisions should be made regarding whether to discontinue nursing or conduct an alternate percutaneous coronary intervention procedure.

## 7.0 ADVERSE EVENTS

### 7.1 Observed Adverse Events

Adverse events observed in the ABSORB family of clinical trials that are related to the key clinical outcomes of death, cardiac death, myocardial infarction (MI) (Q-wave and non-Q-wave), target lesion revascularization (TLR) (by percutaneous coronary intervention [PCI] or coronary artery bypass graft), scaffold thrombosis, ischemia-driven Major Adverse Cardiac Event (MACE) (composite of cardiac death, MI, ischemia-driven TLR [ID-TLR]), and Target Lesion Failure (TLF) (composite of cardiac death, myocardial infarction attributable to target vessel, or ischemia-driven target lesion revascularization) are presented in **Section 8.0 - Clinical Investigations of the Absorb GT1 BVS System**. All other adverse events are included in **Section 7.2 - Adverse Events, Potential Adverse Events**.

### 7.2 Potential Adverse Events

Adverse events that may be associated with PCI, treatment procedures and the use of a coronary scaffold in native coronary arteries include the following, but are not limited to:

[3] Certican® UK label Mar 2015, Afinitor® EU authorization SPC Dec 2014, Votubia® EU SPC Sept 2014, Afinitor® US label Jan 2015, and Zortress® US label Sept 2015. Refer to www.MHRA.gov.uk, www.ema.europa.eu, and www.fda.gov for the most recent versions of these SPC/labels.

- Allergic reaction or hypersensitivity to latex, contrast agent, anesthesia, device materials (platinum, or polymer [poly (L-lactide) (PLLA), polymer poly (D,L-lactide) (PDLLA)]), and drug reactions to everolimus, anticoagulation, or antiplatelet drugs
- Vascular access complications which may require transfusion or vessel repair, including:
    - Catheter site reactions
    - Bleeding (ecchymosis, oozing, hematoma, hemorrhage, retroperitoneal hemorrhage)
    - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture
    - Embolism (air, tissue, plaque, thrombotic material or device)
- Coronary artery complications which may require additional intervention, including:
    - Total occlusion or abrupt closure
    - Arteriovenous fistula, pseudoaneurysm, aneurysm, dissection, perforation / rupture
    - Tissue prolapse / plaque shift
    - Embolism (air, tissue, plaque, thrombotic material or device)
    - Coronary or scaffold thrombosis (acute, subacute, late, very late)
    - Stenosis or restenosis
- Pericardial complications which may require additional intervention, including:
    - Cardiac tamponade
    - Pericardial effusion
    - Pericarditis
- Cardiac arrhythmias (including conduction disorders, atrial and ventricular arrhythmias)
- Cardiac ischemic conditions (including myocardial ischemia, myocardial infarction [including acute], coronary artery spasm and unstable or stable angina pectoris)
- Stroke / Cerebrovascular accident (CVA) and Transient Ischemic Attack (TIA)
- System organ failures:
    - Cardio-respiratory arrest
    - Cardiac failure
    - Cardiopulmonary failure (including pulmonary edema)
    - Renal insufficiency / failure
    - Shock
- Blood cell disorders (including Heparin Induced Thrombocytopenia [HIT])
- Hypotension / hypertension
- Peripheral nerve injury
- Peripheral ischemia
- Infection
- Nausea and vomiting
- Palpitations, dizziness, and syncope
- Chest pain
- Fever
- Pain
- Death

Adverse events associated with daily oral administration of everolimus in doses varying from 1.5 mg to 10 mg daily can be found in the Summary of Product Characteristics (SPC) and labels

for the drug.[4] The risks described below include the anticipated adverse events relevant for the cardiac population referenced in the contraindications, warnings and precaution sections of the everolimus labels / SPCs and / or observed at incidences ≥ 10% in clinical trials with oral everolimus for different indications. Please refer to the drug SPCs and labels for more detailed information and less frequent adverse events.

- Abdominal pain
- Anemia
- Angioedema (increased risk with concomitant ACE inhibitor use)
- Arterial thrombotic events
- Bleeding and coagulopathy (including Hemolytic Uremic Syndrome [HUS], Thrombotic Thrombocytopenic Purpura [TTP], and thrombotic microangiopathy- increased risk with concomitant cyclosporine use)
- Constipation
- Cough
- Diabetes mellitus
- Diarrhea
- Dyspnea
- Embryo-fetal toxicity
- Erythema
- Erythroderma

- Headache
- Hepatic Artery Thrombosis (HAT)
- Hepatic disorders (including hepatitis and jaundice)
- Hypersensitivity to everolimus active substance, or to other rapamycin derivates
- Hypertension
- Infection (bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Polyoma virus-associated nephropathy (PVAN), JC virus associated progressive multiple leukoencephalopathy (PML), fatal infections and sepsis have been reported in patients treated with oral everolimus.)
- Kidney arterial and venous thrombosis
- Laboratory test alterations (elevations of serum creatinine, proteinuria, hypokalemia; hyperglycemia, dyslipidemia including hypercholesterolemia and hypertriglyceridemia; liver function tests abnormal; decreases in hemoglobin, lymphocytes, neutrophils, and platelets)
- Lymphoma and skin cancer
- Male infertility
- Nausea
- Nephrotoxicity (in combination with cyclosporine)
- Non-infectious pneumonitis (including interstitial lung disease)
- Oral ulcerations
- Pain
- Pancreatitis
- Pericardial effusion
- Peripheral edema

[4] Certican® UK label Mar 2015, Afinitor® EU authorization SPC Dec 2014, Votubia® EU SPC Sept 2014, Afinitor® US label Jan 2015, and Zortress® US label Sept 2015. Refer to www.MHRA.gov.uk, www.ema.europa.eu, and www.fda.gov for the most recent versions of these SPC/labels.

- Pleural effusion
- Pneumonia
- Pyrexia
- Rash
- Renal failure
- Upper respiratory tract infection
- Urinary tract infection
- Venous thromboembolism
- Vomiting
- Wound healing complications (including wound infections and lymphocele)

## 8.0 CLINICAL INVESTIGATIONS OF THE ABSORB GT1 BVS SYSTEM

Principal safety and effectiveness information for the Absorb GT1 BVS System is derived from the ABSORB III Randomized Clinical Trial (RCT) and is supported by data from the ABSORB Cohort B clinical trial, ABSORB EXTEND clinical trial, ABSORB II RCT, and ABSORB Japan RCT. In this document, these trials are collectively described as the "ABSORB family of clinical trials" or the "ABSORB trials." An overview of each of the ABSORB trials is presented in **Table 8.0-1**, and results are presented in the following subsections.

The clinical investigations outlined in this section were performed on the previous generation Absorb BVS System. The Absorb GT1 BVS has the same mode of expansion, backbone material, scaffold coating, drug density, permanent scaffold markers, and scaffold design as the Absorb BVS. The Absorb GT1 BVS differs from the Absorb BVS only in the scaffold delivery system. The Absorb GT1 scaffold delivery system utilizes the same principle of operation and materials as other Abbott Vascular RX stent / scaffold systems and coronary dilatation catheters.

Based on the identical nature of the Absorb GT1 scaffold to the Absorb scaffold, performance of the Absorb GT1 BVS can be predicted to be similar to the performance of the Absorb BVS. Within this section, the Absorb BVS and Absorb GT1 BVS System are collectively referred to as "Absorb" and the Absorb BVS and Absorb GT1 BVS are synonymously referred to as the "Absorb scaffold."

**Table 8.0-1: Overview of the ABSORB Family of Clinical Trials**

| | ABSORB III RCT | ABSORB Cohort B | ABSORB EXTEND | ABSORB II RCT | ABSORB JAPAN RCT |
|---|---|---|---|---|---|
| **Study Design** | Multicenter<br>Randomized (2:1)<br>Single-blinded<br>Active-Control | Multicenter<br>Non-randomized<br>First-in-man | Multicenter<br>Non-randomized<br>Continued Assessment | Multicenter<br>Randomized (2:1)<br>Single-blinded<br>Active-Control | Multicenter<br>Randomized (2:1)<br>Single-blinded<br>Active-Control |
| **Numbers of Patients** | Total: 2008 primary analysis population<br>Absorb: 1322<br>XIENCE Control: 686 | Total: 101<br>Group 1: 45<br>Group 2: 56<br>All Absorb | Total: 812<br>All Absorb | Total: 501<br>Absorb: 335<br>XIENCE Control: 166 | Total: 400<br>Absorb: 266<br>XIENCE Control: 134 |
| **Numbers of Enrolling Sites** | 193 sites for primary endpoint analysis population | 12 sites | 56 sites | 46 sites | 38 sites |
| **Study Geography** | US and AUS | AUS, EU, NZ | AP, EU, CA, BZ | EU, NZ | JN |
| **Vessel Sizes and Lesion Lengths** | RVD: ≥ 2.5 and ≤ 3.75 mm<br>Length: ≤ 24 mm | RVD: 3.0 mm<br>Length: ≤ 14 mm | $D_{max}$ ≥ 2.0 mm and $D_{max}$ ≤ 3.3 mm<br>Length: ≤ 28 mm | $D_{max}$ ≥ 2.25 mm and ≤ 3.8 mm<br>Length: ≤ 48 mm | $D_{max}$ ≥ 2.25 mm and ≤ 3.75 mm<br>Length: ≤ 24 mm |
| **# of Lesion Allowed** | Up to two *de novo* lesions in different epicardial vessels.<br>No planned overlap allowed. | Up to two *de novo* lesions in different epicardial vessels.<br>No planned overlap allowed. | Up to two *de novo* lesions in different epicardial vessels.<br>Planned overlap allowed. | Up to two *de novo* lesions in different epicardial vessels.<br>Planned overlap allowed. | Up to two *de novo* lesions in different epicardial vessels.<br>No planned overlap allowed. |
| **Scaffold / Stent Sizes** | Diameter: 2.5, 3.0, 3.5 mm<br>Length: 8, 12, 18, 28 mm | Diameter: 3.0 mm<br>Length: 18 mm | Diameter: 2.5, 3.0, 3.5 mm<br>Length: 12, 18, 28 mm | Diameter: 2.5, 3.0, 3.5 mm<br>Length: 12, 18, 28 mm | Diameter: 2.5, 3.0, 3.5 mm<br>Length: 8, 12, 18, 28 mm |
| **Primary Endpoint(s)** | One-year TLF (non-inferiority) | None | None | • Change in Mean Lumen Diameter from pre- to post-nitrate at 2 years (superiority)<br>• Change in Minimum Lumen Diameter (MLD) at 2 years post-nitrate minus MLD post-procedure post-nitrate (non-inferiority, reflex to superiority) | One-year TLF (non-inferiority) |

| | ABSORB III RCT | ABSORB Cohort B | ABSORB EXTEND | ABSORB II RCT | ABSORB JAPAN RCT |
|---|---|---|---|---|---|
| **Major Secondary Endpoints** | • Angina (powered)<br>• Target Vessel Revascularization (powered)<br>• All revascularization (powered)<br>• Diabetic indication (powered)<br>• Imaging endpoint (powered) | None | None | None | • Late loss at 13 months<br>• Vaso-reactivity at 3-years<br>• Change in MLD at 3-years |
| **Post Procedure Antiplatelet Therapy** | Clopidogrel, prasugrel or ticagrelor 12 months minimum (or ticlopidine per site standard). Aspirin for 5 years. | Clopidogrel 6 months minimum (or ticlopidine per site standard). Aspirin for 5 years. | Clopidogrel, prasugrel or ticagrelor 6 months minimum (or ticlopidine per site standard). Aspirin for 3 years. | Clopidogrel, prasugrel or ticagrelor 6 months minimum (or ticlopidine per site standard). Aspirin for 5 years. | Clopidogrel or prasugrel 12 months minimum (or ticlopidine per site standard). Aspirin indefinitely. |
| **Clinical Follow-ups** | 30, 180 days, annually 1 to 5 years | 30, 180, 270 days, annually 1 to 5 years | 30, 180 days, annually 1 to 3 years | 30, 180 days, annually 1 to 5 years | 30, 180 days, annually 1 to 5 years |
| **Angiographic Follow-up** | 3 years* | Group 1: 180 days, 2 years and 5 years (n = 45)<br>Group 2: 1 year, 3 years, and 5 years (n = 56) | Post-procedure and 2 years* | 2 years | 13 months, 2 to 4 years* |
| **IVUS and / or OCT Follow-up** | 3 years* | Group 1: 180 days, 2 years and 5 years(n = 45)<br>Group 2: 1 year, 3 years and 5 years (n = 56) | Post-procedure and 2 years* | 2 years | 2 to 3 years* |
| **MSCT Follow-up** | None | 18 months | 18 months* | 3 years | 13 months and 3 years* |
| **CTA/SPECT** | N/A | N/A | N/A | N/A | N/A |
| **PK Study** | Yes (12 subjects; US) | None | None | None | None |
| **Status** | Completed enrollment.<br>Follow-up through 1 year completed.<br>Follow-up through 5 years ongoing. | Completed enrollment and follow-up. | Completed enrollment.<br>Follow-up through 1 year completed.<br>Follow-up through 3 years ongoing. | Completed enrollment.<br>Follow-up through 1 year completed.<br>Follow-up through 5 years ongoing. | Completed enrollment.<br>Follow-up through 1 year completed.<br>Follow-up through 5 years ongoing. |

AP, Asia Pacific; AUS, Australia; BZ, Brazil; CA, Canada; EU, Europe; JN, Japan; NZ, New Zealand; US, the United States of America
* Imaging sub-group

## 8.1 ABSORB III Randomized Controlled Trial

The ABSORB III Randomized Controlled Trial (ABSORB III) is the pivotal trial supporting premarket approval of Absorb in the United States. It is a multicenter trial consisting of a lead-in group, a primary analysis group, an imaging cohort, and a pharmacokinetic group.

Enrollment in the ABSORB III primary analysis group is complete and all subjects have completed their 1-year follow-up. Clinical follow-up through 5 years is ongoing. The ABSORB III primary analysis group was analyzed to evaluate Absorb in the primary endpoint of 1-year Target Lesion Failure (TLF) (composite of cardiac death, myocardial infarction attributable to target vessel, or ischemia-driven target lesion revascularization) compared to XIENCE. XIENCE refers to the following commercially available devices: XIENCE V, XIENCE PRIME®, XIENCE Xpedition®, XIENCE Alpine®, XIENCE Pro (outside the US only) and XIENCE Pro$^{X}$ (outside the US only). Results from the primary analysis group are presented below.

Results from the ABSORB III Pharmacokinetic Sub-Study, conducted in a separate and non-randomized cohort of 12 subjects, are presented in **Section 6.2 - Drug Information, Pharmacokinetics**. Enrollment in the lead-in group is complete and the imaging cohort is currently enrolling. The lead-in group and imaging cohort do not contribute to the determination of the ABSORB III primary endpoint, and therefore results from those groups are not presented.

### *8.1.1 Primary Objective*

To evaluate the safety and effectiveness of the Absorb compared to XIENCE.

### *8.1.2 Design*

The ABSORB III primary analysis group is a prospective, randomized (2:1 Absorb to XIENCE), single-blinded, multicenter clinical trial. This trial includes subjects with evidence of myocardial ischemia with stable, unstable angina, post-infarct angina or silent ischemia caused by up to two *de novo* native coronary artery lesions in separate epicardial vessels to coronary artery disease and including patients with diabetes mellitus. Subjects were required to have a lesion length ≤ 24 mm in length and a RVD between 2.5 mm and 3.75 mm. Treatment of one non-target lesion with XIENCE in addition to one target lesion, per assignment, was allowed. The primary analysis group was designed to enroll 2000 subjects at 220 clinical sites in the US and Australia.

Absorb was available in diameters of 2.5, 3.0, and 3.5 mm and lengths of 8, 12, 18, and 28 mm (8 mm not available for 3.5 mm). All commercial sizes and diameters of XIENCE were available except for the 2.25 mm diameter and the 33 and 38 mm lengths. Overlap with the same device as assigned was allowed in the case of bailout.

Clinical follow-up is scheduled at 30 days, 180 days, 1, 2, 3, 4, and 5 years. All subjects received an electrocardiogram (ECG) at 1-year follow-up visit.

Following the index procedure, subjects were to be maintained on a P2Y12 receptor inhibitor for 1 year and aspirin for 5 years.

The primary endpoint of the study is TLF at 1 year, non-inferiority against the control. The primary endpoint is evaluated using the difference in event rates in the intent-to-treat (ITT) population. The hypothesis test is designed to show non-inferiority of Absorb to XIENCE.

The powered secondary endpoints of Angina, All Revascularization and ischemia-driven target

vessel revascularization were evaluated at 1 year in the ITT population and were intended to test for superiority of Absorb to XIENCE.

### *8.1.3 Demographics*

The key baseline demographics and risk factors for the primary analysis group, ITT population, are shown in **Table 8.1.3-1**. A total of 1322 subjects were registered in the Absorb arm and 686 subjects in the XIENCE arm. All baseline characteristics were balanced with no statistical differences between the study arms. Risk factors having a high prevalence in the Absorb and XIENCE arms included hypertension requiring medication (81.0% [1071/1322] and 80.6% [553/686], respectively) and dyslipidemia requiring medication (76.3% [1009/1322] and 77.7% [533/686], respectively). All diabetes mellitus comprised 31.5% (416/1320) and 32.7% (224/686), respectively, and insulin-required diabetes mellitus subjects comprised 10.5% (138/1320) and 11.2% (77/686), respectively. Among diabetics, HbA1c levels for the Absorb and XIENCE arms were 7.56 ± 1.76% and 7.78 ± 2.06%, respectively. Mean body mass index values were 30.58 ± 6.22 and 30.47 ± 6.26, respectively, indicating an overall obese population. For cardiac status, the most common disease presentation in the Absorb and XIENCE arms was stable angina (57.3% [757/1321] and 60.8% [417/686], respectively). Subjects with a single diseased artery were most prevalent in the ABSORB III population (69.5% [919/1322] and 67.2% [461/686], respectively).

**Table 8.1.3-1: Key Baseline Subject Characteristics and Risk Factors – Per-Subject Analysis (Primary Analysis Group, ITT Population)**

| | Absorb (N = 1322) | XIENCE (N = 686) | Difference [95% CI][1] |
|---|---|---|---|
| **Subject Background** | | | |
| Age (year) | 63.5 ± 10.6 (1322) | 63.6 ± 10.3 (686) | -0.2 [-1.1, 0.8] |
| Male Subjects | 70.7% (934/1322) | 70.1% (481/686) | 0.53% [-3.62%, 4.80%] |
| Body Mass Index (kg/m$^2$) | 30.58 ± 6.22 (1322) | 30.47 ± 6.26 (686) | 0.11 [-0.47, 0.69] |
| Current Tobacco Use | 21.3% (281/1322) | 20.7% (142/686) | 0.56% [-3.28%, 4.22%] |
| Any Diabetes Mellitus (DM) | 31.5% (416/1320) | 32.7% (224/686) | -1.14% [-5.49%, 3.12%] |
| DM req. Med. | 28.2% (372/1320) | 28.4% (195/686) | -0.24% [-4.46%, 3.85%] |
| DM req. Insulin | 10.5% (138/1320) | 11.2% (77/686) | -0.77% [-3.77%, 2.01%] |
| HbA1c (%) (All Diabetes Mellitus) | 7.56 ± 1.76 (389) | 7.78 ± 2.06 (209) | -0.22 [-0.55, 0.11] |
| Hypertension req. Med. | 81.0% (1071/1322) | 80.6% (553/686) | 0.40% [-3.15%, 4.12%] |
| Dyslipidemia req. Med. | 76.3% (1009/1322) | 77.7% (533/686) | -1.37% [-5.16%, 2.57%] |
| Prior Coronary Intervention | 38.7% (512/1322) | 38.0% (260/684) | 0.72% [-3.79%, 5.16%] |
| Prior MI | 21.5% (282/1311) | 22.0% (150/681) | -0.52% [-4.42%, 3.23%] |
| **Cardiac Status** | | | |
| AMI | 2.8% (37/1321) | 2.6% (18/686) | 0.18% [-1.49%, 1.59%] |
| Unstable Angina | 26.9% (355/1321) | 24.5% (168/686) | 2.38% [-1.70%, 6.31%] |
| Stable Angina | 57.3% (757/1321) | 60.8% (417/686) | -3.48% [-7.96%, 1.07%] |
| Silent Ischemia | 10.0% (132/1321) | 10.2% (70/686) | -0.21% [-3.12%, 2.47%] |
| No Current Evidence of Ischemia | 2.1% (28/1321) | 1.3% (9/686) | 0.81% [-0.52%, 1.92%] |
| Single diseased artery | 69.5% (919/1322) | 67.2% (461/686) | 2.31% [-1.93%, 6.65%] |
| Two diseased arteries | 24.3% (321/1322) | 26.4% (181/686) | -2.10% [-6.19%, 1.85%] |
| Three or more diseased arteries | 6.2% (82/1322) | 6.4% (44/686) | -0.21% [-2.61%, 1.94%] |

[1] By normal approximation for continuous variables and Newcombe score method for binary variables
**Note:** N is the total number of subjects

### *8.1.4 Results*

ABSORB III met the primary endpoint. The TLF rate at 1 year was 7.8% (102/1313) in the Absorb arm and 6.1% (41/677) in the XIENCE arm. The difference between the two treatment arms was 1.71% with the 97.5% upper confidence limit being 3.93%, which was less than the non-inferiority margin of 4.5%. The Absorb arm was non-inferior to XIENCE with a non-inferiority p-value of 0.0070 for TLF rates at 1 year (**Table 8.1.4-1**). These analyses are based on the ITT population.

**Table 8.1.4-1: Primary Endpoint Analysis – Per-Subject Analysis (Primary Analysis Group, ITT, Per-Protocol MI Definition)**

| | Absorb (N = 1322) | XIENCE (N = 686) | Difference (Upper One-Sided 97.5% CL[1]) | Non-Inferiority p-value[2] |
|---|---|---|---|---|
| **1-Year TLF (Cardiac Death Target Vessel MI, ID-TLR)** | 7.8% (102/1313) | 6.1% (41/677) | 1.71% (3.93%) | 0.0070 |

[1] One-sided upper 97.5% confidence limit by Farrington-Manning method
[2] One-sided p-value by using Farrington-Manning non-inferiority test statistic with non-inferiority margin of 4.5%, to be compared with a one-sided significance level of 0.025
**Note:** 1-year timeframe includes a window of ± 28 days
**Note:** N is the total number of subjects
**Note:** MI is per ABSORB III protocol definition

The analyses of Angina, All Revascularization, and ID-TVR at 1 year for the ITT population are shown in **Table 8.1.4-2**. Superiority was not met for any of the powered secondary endpoints. Absorb showed similar rates to XIENCE in 1 year Angina, All Revascularization, and ID-TVR. The Angina rate at 1 year was 18.3% (238/1303) in the Absorb arm and 18.4% (125/678) in the XIENCE arm (p = 0.9256). The All Revascularization rate at 1 year was 9.1% (120/1313) in the Absorb arm and 8.1% (55/677) in the XIENCE arm (p = 0.5040). The ID-TVR rate at 1 year was 5.0% (66/1313) in the Absorb arm and 3.7% (25/677) in the XIENCE arm (p = 0.2126).

**Table 8.1.4-2: Powered Secondary Endpoint Analysis – Per-Subject Analysis (Primary Analysis Group, ITT Population)**

| | Absorb (N = 1322) | XIENCE (N = 686) | Difference [95% CL][4] | Superiority p-value[5] |
|---|---|---|---|---|
| **Powered Secondary Endpoint** | | | | |
| **1-Year Angina**[1] | 18.3% (238/1303) | 18.4% (125/678) | -0.17% [-3.77%, 3.42%] | 0.9256 |
| **1-Year All Revascularization**[2] | 9.1% (120/1313) | 8.1% (55/677) | 1.02% [-1.57%, 3.60%] | 0.5040 |
| **1-Year ID-TVR**[3] | 5.0% (66/1313) | 3.7% (25/677) | 1.33% [-0.51%, 3.18%] | 0.2126 |

[1] First reported angina post-discharge. Excluding angina following the index procedure through discharge, not to exceed a period of 7 days.
[2] Includes TLR, TVR excluding TLR, and non TVR
[3] Ischemia-driven target vessel revascularization
[4] For the powered secondary endpoint of Angina, Pearson's Chi-square two-sided 95% confidence interval. For the powered secondary endpoints of All Revascularization and ID-TVR, exact two-sided 95% confidence interval.
[5] To be compared with a two-sided significance level of 0.05. For the powered secondary endpoint of Angina, two-sided p-value by using Pearson's Chi-square test statistic. For the powered secondary endpoints of All Revascularization and ID-TVR, two-sided p-value by using Fisher's exact test statistic.
**Note:** 1-year timeframe includes a window of ± 28 days
**Note:** N is the total number of subjects

The safety and efficacy results for ABSORB III primary analysis group are presented in **Table 8.1.4-3**. Absorb and XIENCE were not statistically different in the safety and efficacy endpoints at 1 year.

**Table 8.1.4-3: ABSORB III Clinical Results (Primary Analysis Group - ITT Population) through 1 Year**

| | Absorb (N = 1322) | XIENCE (N = 686) | Difference [95% CI][1] |
|---|---|---|---|
| **COMPOSITE EFFICACY AND SAFETY** | | | |
| TLF | 7.8% (102/1313) | 6.1% (41/677) | 1.71% [-0.74%, 3.93%] |
| **EFFICACY** | | | |
| Ischemia-Driven TLR | 3.0% (40/1313) | 2.5% (17/677) | 0.54% [-1.14%, 1.96%] |
| TLR, CABG | 0.2% (3/1313) | 0.4% (3/677) | -0.21% [-1.08%, 0.31%] |
| TLR, PCI | 2.8% (37/1313) | 2.2% (15/677) | 0.60% [-1.00%, 1.96%] |
| Ischemia-Driven TVR | 5.0% (66/1313) | 3.7% (25/677) | 1.33% [-0.67%, 3.10%] |
| **SAFETY** | | | |
| All Death | 1.1% (15/1313) | 0.4% (3/677) | 0.70% [-0.26%, 1.49%] |
| Cardiac Death | 0.6% (8/1313) | 0.1% (1/677) | 0.46% [-0.29%, 1.06%] |
| Vascular Death | 0.2% (2/1313) | 0.0% (0/677) | 0.15% [-0.42%, 0.55%] |
| Non-cardiovascular Death | 0.4% (5/1313) | 0.3% (2/677) | 0.09% [-0.72%, 0.64%] |
| All MI | 6.9% (90/1313) | 5.6% (38/677) | 1.24% [-1.11%, 3.36%] |
| TV-MI | 6.0% (79/1313) | 4.6% (31/677) | 1.44% [-0.74%, 3.39%] |
| QMI | 0.7% (9/1313) | 0.3% (2/677) | 0.39% [-0.45%, 1.04%] |
| NQMI | 5.3% (70/1313) | 4.3% (29/677) | 1.05% [-1.06%, 2.91%] |
| NTV-MI | 0.8% (11/1313) | 1.2% (8/677) | -0.34% [-1.54%,0.53%] |
| QMI | 0.1% (1/1313) | 0.1% (1/677) | -0.07% [-0.76%, 0.30%] |
| NQMI | 0.8% (10/1313) | 1.0% (7/677) | -0.27% [-1.41%, 0.56%] |
| Cardiac Death or MI | 7.5% (98/1313) | 5.8% (39/677) | 1.70% [-0.70%, 3.87%] |
| **Cumulative ARC-defined Definite + Probable Stent / Scaffold Thrombosis (0-393 days)** | 1.54% (20/1301) | 0.74% (5/675) | 0.80% [-0.32%, 1.72%] |
| Acute (≤ 1 day) | 0.15% (2/1320) | 0.58% (4/686) | -0.43% [-1.34%, 0.10%] |
| Sub-Acute (> 1-30 days) | 0.91% (12/1315) | 0.15% (1/686) | 0.77% [-0.01%, 1.45%] |
| Late (31-365 days) | 0.46% (6/1299) | 0.00% (0/675) | 0.46% [-0.16%, 1.00%] |
| Very Late (> 365-393 days) | 0.00% (0/1299) | 0.00% (0/675) | 0.00% [-0.57%, 0.29%] |

[1] By Newcombe score method
**Note:** 1-year timeframe includes a window of ± 28 days
**Note:** N is the total number of subjects
**Note:** MI is per protocol definition

### Analysis Stratified by Reference Vessel Diameter (RVD) Size

In the ABSORB III trial, the pre-procedure RVD defined in the protocol was ≥ 2.5 mm to ≤ 3.75 mm by visual estimation / site assessment. With Absorb being a slightly larger device compared to XIENCE, a post-hoc analysis by RVD was conducted using the RVD cut-off of ≥ 2.25 mm versus < 2.25 mm (by QCA). The 2.25 mm cut-off was chosen based on the lower bound RVD criteria in the ABSORB III trial being 2.5 mm and QCA's underestimation of visual assessment by ~0.25 mm. **Table 8.1.4-4** provides the key clinical results by the RVD subgroups of ≥ 2.25 mm (by QCA) and < 2.25 mm (by QCA). In the ABSORB III trial, 81% of the population had a RVD ≥ 2.25 mm (by QCA). In RVD ≥ 2.25 mm (by QCA) subgroup, both the Absorb and XIENCE arms performed similarly to the overall ABSORB III population. In the RVD ≥ 2.25 mm

(by QCA) subgroup, the TLF rate was low and similar between Absorb and XIENCE. The TLF rates in the overall population were 7.8% for Absorb and 6.1% for XIENCE. The difference between the two arms was less in the RVD ≥ 2.25 mm (by QCA) subgroup than that in the overall ABSORB III population (1.2% vs. 1.7%, respectively). Additionally, in the RVD ≥ 2.25 mm (by QCA) subgroup, the ST rate was low and similar between Absorb (0.9%) and XIENCE (0.6%) and the difference in ST between the two arms was less than that in the overall ABSORB III population (0.3% vs. 0.8%, respectively).

**Table 8.1.4-4** also presents the clinical outcomes for the subgroup with pre-procedure RVD < 2.25 mm (by QCA). Although visually estimated by investigators to be ≥ 2.5 mm, subjects with RVD < 2.25 mm (by QCA) made up 19% of the overall ABSORB III population. The event rates were higher in both the Absorb and the XIENCE arms in the RVD < 2.25 mm (by QCA) subgroup, as compared to both the overall ABSORB III population and RVD ≥ 2.25 mm (by QCA) subgroup.

**Table 8.1.4-4: Clinical Results for ABSORB III Stratified by Pre-Procedure RVD Size - RVD ≥ 2.25 mm and RVD < 2.25 mm by QCA (ITT population) – 1-Year Results**

| | Subjects with RVD ≥ 2.25 mm | | Subjects with RVD < 2.25 mm* | |
|---|---|---|---|---|
| | **Absorb (N = 1074)** | **XIENCE (N = 549)** | **Absorb (N = 242)** | **XIENCE (N = 133)** |
| **Percentage of Subjects** | 81.6% (1074/1316) | 80.5% (549/682) | 18.4% (242/1316) | 19.5% (133/682) |
| **Pre-procedure Median RVD by QCA (mm) Range (min, max)** | 2.75 (2.25, 4.04) | 2.72 (2.26, 4.48) | 2.08 (1.39, 3.54) | 2.10 (1.46, 3.49) |
| **TLF** | 6.7% (71/1067) | 5.5% (30/542) | 12.9% (31/241) | 8.3% (11/133) |
| **Cardiac Death** | 0.6% (6/1067) | 0.2% (1/542) | 0.8% (2/241) | 0.0% (0/133) |
| **TV- MI** | 5.2% (55/1067) | 4.6% (25/542) | 10.0% (24/241) | 4.5% (6/133) |
| **ID-TLR** | 2.2% (24/1067) | 1.5% (8/542) | 6.6% (16/241) | 6.8% (9/133) |
| **Stent / Scaffold Thrombosis (Def / Prob)** | 0.9% (9/1058) | 0.6% (3/540) | 4.6% (11/238) | 1.5% (2/133) |

**Note:** N is the total number of subjects
**Note:** MI is per protocol definition
* The ITT subjects with at least one target lesion pre-procedure RVD < 2.25 mm (core-lab measurement) are included in the analysis.

## 8.2 Analysis of Diabetic Subjects in ABSORB III

The diabetic patient population is at high risk for cardiovascular morbidity and mortality and is associated with worse clinical outcomes when undergoing PCI. In the ABSORB III trial, diabetic patients represented 31.9% (640/2006) of the overall trial population. The 1-year rates of TLF, non-hierarchically assessed cardiac death, TV-MI and ID-TLR, and stent/scaffold thrombosis for the overall population, all diabetes mellitus (all DM) subgroup ,and all non-DM subgroup are

shown in **Table 8.2-1**.

For the all DM subgroup, the observed clinical event rates in both Absorb and XIENCE arms were higher than in the overall population and non-DM subgroup for most key outcome measures. For most endpoints, the % increase in event rates from the overall population to the diabetic population is similar between the two arms. For the all non-DM subgroup, the observed clinical event rates in both arms were lower than in the overall population for most key outcome measures. The only exception to this pattern was in cardiac death, which in both arms was nearly unchanged between the overall population and both subgroups. For the DM subgroup, non-DM subgroup, and the overall population, there were no statistical differences for any endpoint comparisons between study arms.

**Table 8.2-1 Subgroup Information and 1-Year Clinical Outcomes Stratified by Diabetic Status – Per-Subject Analysis (Primary Analysis Group, Intent-to-Treat Population, Per Protocol MI Definition)**

| | All DM | | All non-DM | |
|---|---|---|---|---|
| | **Absorb (N=416)** | **XIENCE (N=224)** | **Absorb (N=904)** | **XIENCE (N=462)** |
| **TLF** | 10.7% (44/411) | 9.1% (20/220) | 6.3% (57/900) | 4.6% (21/457) |
| **Cardiac Death** | 0.5% (2/411) | 0.0% (0/220) | 0.7% (6/900) | 0.2% (1/457) |
| **TV- MI** | 9.0% (37/411) | 7.3% (16/220) | 4.6% (41/900) | 3.3% (15/457) |
| **ID-TLR** | 5.6% (23/411) | 3.6% (8/220) | 1.8% (16/900) | 2.0% (9/457) |
| **Stent/Scaffold Thrombosis (Def/Prob)** | 3.2% (13/405) | 1.4% (3/219) | 0.8% (7/894) | 0.4% (2/456) |

The Absorb arm of the diabetic subgroup had a higher observed 1 year scaffold thrombosis rate compared to Xience. Further analysis identified that approximately 70% of the ST in both arms occurred in very small vessels (< 2.25 mm), outside of the intended indication. In the ≥ 2.25 mm subgroup, device thrombosis rates were 1.3% for Absorb (4/318) and 0.6% for XIENCE (1/173).

## 8.3 ABSORB Cohort B

The ABSORB Cohort B trial is a prospective, single-arm, open-label, multicenter, international clinical study intended to assess the safety and performance of ABSORB Cohort B Device in the treatment of patients with *de novo* native coronary artery lesions. The ABSORB Cohort B Device is a previous generation of the Absorb GT1 BVS System utilizing a similar Absorb scaffold.

### *8.3.1 Primary Objective*

To assess the safety and performance of the Absorb in the treatment of subjects with a maximum of two *de novo* native coronary artery lesions located in two different major epicardial vessels.

### *8.3.2 Design*

A total of 101 subjects were enrolled at 12 clinical sites located in Europe, Australia, and New Zealand.

Subjects with up to two *de novo* native coronary artery lesions in separate epicardial vessels with visually estimated nominal vessel diameters of 3.0 mm and lesion(s) length ≤ 14 mm were enrolled, and received a single 3.0 x 18 mm Absorb per lesion treated.

Subjects were evaluated at 30 days, 180 days, 270 days, 12 months, 18 months (subset), 2 years, 3 years, 4 years and 5 years. Subjects in the first group (B1) had invasive imaging with qualitative coronary angiography, IVUS, IVUS-VH, and OCT at 6 months, 2 years and 5 years while the second group (B2) had these invasive imaging at 12 months, 3 years and 5 years. Vasomotor function test using nitroglycerin was done at 2, 3 and 5 year follow-up. A MSCT scan was mandatory for a subset of subjects at 18 months and at 5 years.

### *8.3.3 Demographics*

The mean age of the full Cohort B subjects (ITT population) was 62.3 years. 72.3% of subjects were men and 17.0% of subjects were current smokers. Diabetic subjects comprised 16.8% of the overall population. Subjects with hypertension, hypercholesterolemia, and a family history of coronary artery disease comprised 66.0%, 85.1%, and 54.6% of the subject population, respectively. Subjects with prior MI made up 25.0% of the population and 21.8% of subjects had a prior cardiac intervention. Subjects with unstable angina at the time of the index procedure made up 14.9% of the population. There were 20.8% of subjects who had multi-vessel disease.

### *8.3.4 Clinical Results for ABSORB Cohort B*

**Table 8.3.4-1** shows clinical outcomes through 5 years for all subjects (n = 101) in the ABSORB Cohort B trial. The hierarchical MACE rate was 11.0% (11/100) at 5 years. The overall MI rate at 5 years was 3.0% (3/100), all due to NQMI occurring within 6 months. There were no additional MI events after 6 months up to 5 years. The overall ID-TLR rate at 5 years was 8.0% (8/100). Between 4 and 5 years there was only one additional ID-TLR event that occurred. There were no cardiac deaths or scaffold thrombosis events during the entire 5-year follow-up period. In the ABSORB Cohort B clinical investigation, Absorb showed excellent long-term clinical outcomes with low MACE rates out to 5 years with absence of cardiac death, Q wave MI, and scaffold thrombosis.

## Table 8.3.4-1: Key Clinical Outcomes of ABSORB Cohort B (ITT Population) through 5 Years

| | Absorb 30 days (N = 101) | Absorb 6 months (N = 101) | Absorb 1 year (N = 101) | Absorb 2 year (N = 100*) | Absorb 3 year (N = 100*) | Absorb 4 year (N = 100*) | Absorb 5 year (N = 100*) |
|---|---|---|---|---|---|---|---|
| **COMPOSITE EFFICACY AND SAFETY** | | | | | | | |
| MACE | 2.0% (2/101) | 5.0% (5/101) | 6.9% (7/101) | 9.0% (9/100) | 10.0% (10/100) | 10.0 (10/100) | 11.0 (11/100) |
| **EFFICACY** | | | | | | | |
| Ischemia-Driven TLR | 0.0% (0/101) | 2.0% (2/101) | 4.0% (4/101) | 6.0% (6/100) | 7.0% (7/100) | 7.0% (7/100) | 8.0% (8/100) |
| TLR, CABG | 0.0% (0/101) | 0.0% (0/101) | 0.0% (0/101) | 0.0% (0/100) | 0.0% (0/100) | 0.0% (0/100) | 0.0% (0/100) |
| TLR, PCI | 0.0% (0/101) | 2.0% (0/101) | 4.0% (4/101) | 6.0% (6/100) | 7.0% (7/100) | 7.0% (7/100) | 8.0% (8/100) |
| Ischemia-Driven TVR | 0.0% (0/101) | 2.0% (2/101) | 4.0% (4/101) | 8.0% (8/100) | 10.0% (10/100) | 10.0% (10/100) | 11.0% (11/100) |
| **SAFETY** | | | | | | | |
| Cardiac Death | 0.0% (0/101) | 0.0% (0/101) | 0.0% (0/101) | 0.0% (0/100) | 0.0% (0/100) | 0.0% (0/100) | 0.0% (0/100) |
| All MI | 2.0% (2/101) | 3.0% (3/101) | 3.0% (3/101) | 3.0% (3/100) | 3.0% (3/100) | 3.0% (3/100) | 3.0% (3/100) |
| QMI | 0.0% (0/101) | 0.0% (0/101) | 0.0% (0/101) | 0.0% (0/100) | 0.0% (0/100) | 0.0% (0/100) | 0.0% (0/100) |
| NQMI | 2.0% (2/101) | 3.0% (3/101) | 3.0% (3/101) | 3.0% (3/100) | 3.0% (3/100) | 3.0% (3/100) | 3.0% (3/100) |
| Scaffold Thrombosis | 0.0% (0/101) | 0.0% (0/101) | 0.0% (0/101) | 0.0% (0/95) | 0.0% (0/95) | 0.0% (0/95) | 0.0% (0/95) |

*One subject lost to follow-up at 2-year follow-up.
**Note:** MACE: Cardiac death, MI, ischemia-driven TLR
**Note:** MI per protocol definition
**Note:** Follow-up windows were: 30 days ± 7 days; 6 months ± 14 days; 1 year ± 28 days; 2 year ± 2 months; 3 year ± 28 days; 4 year ± 28 days; 5 year ± 28 days

### *8.3.5 Intravascular Ultrasound (IVUS) Outcomes*

**Cohort B1:** Paired IVUS data at post-procedure, 6-month, 2-year, and 5-year follow-up were available for 21 lesions from Group 1 subjects (**Table 8.3.5-1**). Average plaque area increased significantly from post-procedure to 6 months (7.81 $mm^2$ to 8.33 $mm^2$, p = 0.0140). However, the average vessel, lumen and scaffold area remained comparable between baseline and 6 months. From 6 months to 2 years there were significant increases in vessel area (14.92 $mm^2$ to 15.88 $mm^2$, p = 0.0009) and scaffold area (6.63 $mm^2$ to 7.52 $mm^2$, p < 0.0001). These enlargements were accompanied by late increased average lumen area (6.59 $mm^2$ vs. 7.24 $mm^2$, p = 0.0153). These results indicate a late lumen expansion with Cohort B Device implantation. At 5 years, scaffold area was no longer identifiable from IVUS imaging. There was a significant reduction in plaque area from 2 to 5 years (8.64 $mm^2$ vs. 7.75 $mm^2$, p = 0.0005), but the average lumen area remained stable (7.24 $mm^2$ vs. 7.46 $mm^2$, p = 0.2774).

**Table 8.3.5-1: Paired IVUS Results at Post-Procedure, 6 Month, 2 Year, and 5 Year (Group 1, ITT Population)**

| | Post-procedure (L = 21) | 6-Month (L = 21) | 2-Year (L = 21) | 5-Year (L = 21) | p-value (post vs. 6M)* | p-value (6M vs. 2Y)* | p-value (2Y vs. 5Y)* |
|---|---|---|---|---|---|---|---|
| **Average Vessel Area ($mm^2$)** | 14.56 ± 3.82 | 14.92 ± 3.78 | 15.88 ± 4.02 | 15.28 ± 4.53 | 0.0957 | 0.0009 | 0.0785 |
| **Average Scaffold Area ($mm^2$)** | 6.75 ± 1.19 | 6.63 ± 1.16 | 7.52 ± 1.79 | N/A | 0.1754 | < 0.0001 | N/A |
| **Average Lumen Area ($mm^2$)** | 6.75 ± 1.19 | 6.59 ± 1.20 | 7.24 ± 1.91 | 7.46 ± 2.45 | 0.0850 | 0.0153 | 0.2774 |
| **Average Plaque Area ($mm^2$)** | 7.81 ± 2.98 | 8.33 ± 2.88 | 8.64 ± 2.85 | 7.75 ± 2.62 | 0.0140 | 0.0696 | 0.0005 |

* Paired comparisons between the different time points were done by a Wilcoxon's signed rank test for continuous variables.
**Note:** Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.
**Note:** Follow-up windows were: 6 months ± 14 days; 2 year ± 2 months; 5 year ± 28 days

**Cohort B2:** Paired IVUS data at post-procedure, 1-year, 3-year, and 5-year follow-up were available for 30 lesions from Group 2 subjects (**Table 8.3.5-2**). There was a modest but significant increase in total plaque area (7.30 $mm^2$ to 7.84 $mm^2$, p = 0.0095) with concomitant non-significant increase in vessel area. Average scaffold and lumen area remain unchanged through 1 year. From 1 to 3 years, both scaffold area and lumen area increased significantly (6.37 $mm^2$ vs. 7.05 $mm^2$, p < 0.0001; and 6.31 $mm^2$ vs. 6.70 $mm^2$, p = 0.0028, respectively). The late lumen enlargement is of particular interest because the vessel area was preserved (14.15 $mm^2$ at 1 year vs. 14.25 $mm^2$ at 3 years, p = 0.4560). The late lumen enlargement observed by IVUS from 1 year to 3 years in Group 2 is consistent with the trends noted previously between 6 months and 2 years in Group 1 and reinforces the unique properties of the bioresorbable scaffold. At 5 years, scaffold area was no longer identifiable from IVUS imaging. The average vessel area and plaque area decreased from 3 to 5 years, and the average lumen area remained comparable to that at 3 years (6.48 $mm^2$ vs. 6.70 $mm^2$, p = 0.1838).

**Table 8.3.5-2: Paired IVUS Results at Post-Procedure, 1, 3, and 5 Year (Group 2, ITT Population)**

| | Post-procedure (L = 30) | 1-Year (L = 30) | 3-Year (L = 30) | 5-Year (L = 28) | p-value (post vs. 1Y)* | p-value (1Y vs. 3Y)* | p-value (3Y vs. 5Y)* |
|---|---|---|---|---|---|---|---|
| **Average Vessel Area ($mm^2$)** | 13.61 ± 2.40 | 14.15 ± 2.61 | 14.25 ± 2.57 | 13.23 ± 2.70 | 0.0629 | 0.4560 | 0.0003 |
| **Average Scaffold Area ($mm^2$)** | 6.31 ± 0.86 | 6.37 ± 0.97 | 7.05 ± 1.39 | N/A | 0.8646 | < 0.0001 | N/A |
| **Average Lumen Area ($mm^2$)** | 6.31 ± 0.86 | 6.31 ± 1.01 | 6.70 ± 1.48 | 6.48 ± 1.50 | 0.4199 | 0.0028 | 0.1838 |
| **Average Plaque Area ($mm^2$)** | 7.30 ± 1.85 | 7.84 ± 1.92 | 7.55 ± 1.58 | 6.79 ± 1.90 | 0.0095 | 0.0514 | 0.0001 |

* Paired comparisons between the different time points were done by a Wilcoxon's signed rank test for continuous variables.
**Note:** Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.
**Note:** Follow-up windows were: 1 year ± 28 days; 3 year ± 28 days; 5 year ± 28 days

In both ABSORB Cohort B1 and B2, Absorb demonstrated good patency out to 5 years.

### *8.3.6 Optical Coherence Tomography (OCT) Analysis*

**Cohort B1:** Serial OCT analysis at baseline, 6 months, 2 and 5 years were available in 13 lesions from Group 1 (**Table 8.3.6-1**). There were no significant changes in the mean scaffold area between post-procedure and 6 months. At 6-month follow-up, the neointima located between and over the struts represents a surface area of 1.53 $mm^2$. As a result, the mean and minimal luminal area and flow area decreased significantly. Strut coverage was almost complete (~98%) at 6 month follow-up. From 6 months to 2 years the mean strut core area continued to decrease from 0.22 $mm^2$ to 0.15 $mm^2$ (p = 0.0012), indicating continued strut bioresorption. The mean scaffold area increased from post-procedure (7.55 $mm^2$) to 2 years (8.54 $mm^2$, p = 0.0171) indicating loss of mechanical integrity of the scaffold and potential expansion of the vessel. As a result, mean lumen area remain unchanged despite the minimal increase in mean neointimal area from 6 months to 2 years (1.53 $mm^2$ vs. 2.22 $mm^2$, p = 0.0012). Between 2 and 5 years, mean luminal and flow areas remain comparable. At 5-year follow-up, all struts have completely resorbed; therefore, scaffold area cannot be assessed.

**Table 8.3.6-1: Paired OCT Results at Post-Procedure, 6 Months, 2 and 5 Years (Group 1, ITT Population)**

| Group 1 OCT (paired) | Post-procedure (L = 13) | 6-Month (L = 13) | 2-Year (L = 13) | 5-Year (L = 13) | p-value post vs. 6M* | p-value 6M vs. 2Y* | p-value post vs. 2Y* | p-value 2Y vs. 5Y* |
|---|---|---|---|---|---|---|---|---|
| **Mean Neointimal Area ($mm^2$)** | N/A | 1.53 ± 0.36 | 2.22 ± 0.47 | N/A | N/A | 0.0012 | N/A | N/A |
| **Mean Strut Core Area ($mm^2$)** | 0.22 ± 0.03 | 0.22 ± 0.06 | 0.15 ± 0.02 | N/A | 0.8926 | 0.0012 | 0.0002 | N/A |
| **% of Uncovered Struts** | 96.97 ± 6.83 | 1.80 ± 1.63 | 1.40 ± 2.37 | N/A | 0.0002 | 0.1909 | 0.0002 | N/A |

* Paired comparisons between the different time points were done by a Wilcoxon's signed rank test for continuous variables.
**Note:** Data are presented as Mean ± SD or %. L is the number of lesions with a paired measurement for the specific variable.
**Note:** Follow-up windows were: 6 months ± 14 days; 2 year ± 2 months; 5 year ± 28 days

**Cohort B2:** Serial OCT imaging at baseline, 1, 3 and 5 years were available in 17 lesions from Group 2 (**Table 8.3.6-2**). There were no significant changes in mean and minimal scaffold area between post-procedure and 1 year although the strut core area decreased significantly from 0.19 $mm^2$ to 0.16 $mm^2$ (an optical sign of bioresorption). The neointimal growth was low and well controlled at 1.42 $mm^2$; as a result, there was a minimal reduction in the functional lumen at 1 year as demonstrated by the decrease in mean and minimal flow area as well as an increase in lumen area stenosis from immediately post-procedure to 1 year. The OCT analysis revealed scaffold enlargement between 1 year and 3 years (mean scaffold area of 7.45 $mm^2$ at 1 year vs. 8.61 $mm^2$ at 3 years, p = 0.0003) consistent with IVUS results. Lumen area remained fairly constant, despite the minimal increase in neointimal hyperplasia at 3 years (mean neointimal area of 1.42 $mm^2$ at 1 year vs. 2.39 $mm^2$ at 3 years, p < 0.0001). Strut coverage was almost complete at 1 year (~97%), which was further increased to ~98% at 3 years. Mean luminal and flow areas remain stable from 3 to 5 years. At 5-year follow-up, struts were no longer identifiable in any Group 2 patients, suggesting complete bioresorption.

**Table 8.3.6-2: Paired OCT Results at Post-Procedure, 1, 3 and 5 Years (Group 2, ITT Population)**

| Group 2 OCT (paired) | Post-procedure (L = 17) | 1-Year (L = 17) | 3-Year (L = 17) | 5-Year (L = 17) | p-value post vs. 1Y* | p-value 1Y vs. 3Y* | p-value post vs. 3Y* | p-value 3Y vs. 5Y* |
|---|---|---|---|---|---|---|---|---|
| **Mean Neointimal Area ($mm^2$)** | N/A | 1.42 ± 0.71 | 2.39 ± 0.68 | N/A | N/A | < 0.0001 | N/A | N/A |
| **Mean Strut Core Area ($mm^2$)** | 0.19 ± 0.03 | 0.16 ± 0.02 | 0.20 ± 0.03 | N/A | 0.0079 | 0.0002 | 0.4307 | N/A |
| **% of Uncovered Struts** | 97.65 ± 5.56 | 3.03 ± 2.81 | 1.70 ± 1.59 | N/A | < 0.0001 | 0.0131 | < 0.0001 | N/A |

* Paired comparisons between the different time points were done by a Wilcoxon's signed rank test for continuous variables
**Note:** Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.
**Note:** Follow-up windows were: 1 year ± 28 days; 3 year ± 28 days; 5 year ± 28 days.

### *8.3.7 Multi-Slice Computed Tomography (MSCT) Analysis (Full cohort)*

Unlike metal stents where visualization or evaluation of the in-stent lumen by MSCT is challenging owing to the blooming artifact caused by metallic stent struts, it was possible to assess quantitatively the scaffolded segment in 61 lesions in Cohort B at 18 months. MSCT allowed non-invasive assessment of segments treated with Absorb scaffold and demonstrated no significant restenosis with % area stenosis of 22.73 ± 22.41% and mean lumen area of 5.15 ± 1.35 mm² (**Table 8.3.7-1**).

**Table 8.3.7-1: Key MSCT of ABSORB Cohort B (ITT Population)**

| | **18 Months (L = 61)** |
|---|---|
| Mean Vessel Area ($mm^2$) | 14.09 ± 4.29 |
| Mean Lumen Area ($mm^2$) | 5.15 ± 1.35 |
| Mean Plaque Area ($mm^2$) | 8.94 ± 3.41 |
| Area Stenosis (%) | 22.73 ± 22.41 |

**Note:** Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.
**Note:** Follow-up window was: 18 months ± 28 days

Unlike permanent metal implants, polymeric implants do not cause imaging artifacts during non-invasive CT or MR evaluation. The data from ABSORB Cohort B demonstrates that Absorb provides the additional benefit that a polymeric bioresorbable scaffold may be more compatible with the growing usage of non-invasive follow-up imaging than is the case with metallic stents. Potentially this may facilitate patient management and provide economic benefits.

### *8.3.8 Vasomotor Function Outcomes*

The 5-year data demonstrated significantly improved vasomotor function at the 3-year and 5-year follow-up. At the 3-year follow-up, 27 patients from Group 2 underwent vasomotor function test with nitrate administration (**Table 8.3.8-1**). The in-scaffold mean lumen diameter increased from 2.45 ± 0.37 mm (pre-nitrate) to 2.50 ± 0.39 mm (post-nitrate) (p = 0.0050). At the 5-year follow-up, a total of 57 patients from the full Cohort B (23 from Group 1 and 34 from Group 2) completed vasomotor function tests with nitrate administration (**Table 8.3.8-1**). The in-scaffold mean lumen diameter increased from 2.48 ± 0.38 mm (pre-nitrate) to 2.56 ± 0.37 mm (post-nitrate) (p < 0.0001). These data indicate that with vessel healing and the gradual disappearance of the scaffold, the treated segment is free to respond to physiologic stimuli.

**Table 8.3.8-1: Vasomotor Function by Nitroglycerine Injection at 2, 3 and 5 Years (PTE Population)**

| | **Mean Luminal Diameter (mm)** | | | | | | **p-values*, Pre vs. Post** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Group B1 2 Y (L = 33)** | | **Group B2 3 Y (L = 47)** | | **Full Cohort 5 Y (L = 57)** | | **2Y** | **3Y** | **5Y** |
| | **Pre-NTG** | **Post-NTG** | **Pre-NTG** | **Post-NTG** | **Pre-NTG** | **Post-NTG** | | | |
| Proximal | 2.48 ± 0.46 | 2.65 ± 0.42 | 2.51 ± 0.39 | 2.63 ± 0.48 | 2.53 ± 0.44 | 2.64 ± 0.43 | 0.0018 | 0.0065 | < 0.0001 |
| Distal | 2.26 ± 0.41 | 2.40 ± 0.40 | 2.28 ± 0.33 | 2.41 ± 0.35 | 2.26 ± 0.41 | 2.39 ± 0.39 | 0.0002 | < 0.0001 | < 0.0001 |
| Scaffold | 2.44 ± 0.37 | 2.47 ± 0.35 | 2.45 ± 0.37 | 2.50 ± 0.39 | 2.48 ± 0.38 | 2.56 ± 0.37 | 0.0352 | 0.0050 | < 0.0001 |

* Paired comparisons between the different time points were done by a Wilcoxon's signed rank test for continuous variables.
**Note:** Data are presented as Mean ± SD. L is the number of lesions with a paired measurement for the specific variable.

## 8.4 ABSORB EXTEND

The ABSORB EXTEND trial was established to expand treatment with Absorb in a broader patient population around the world, to collect clinical data with minimum follow-up imaging, and to increase lesion complexity by including subjects with longer lesions treated with either overlapping of two Absorb or use of longer length Absorb.

### *8.4.1 Primary Objective*

To continue the assessment of the safety and performance of Absorb in a population of up to 1,000 subjects with a maximum of two *de novo* native coronary artery lesions each located in different epicardial vessels.

### *8.4.2 Design*

ABSORB EXTEND is a prospective, single-arm, open-label clinical study that registered approximately 812 subjects at up to 56 global sites. Subjects with a maximum of two *de novo* native coronary artery lesions each located in different epicardial vessels, a target lesion length ≤ 28 mm and a reference vessel sizes that were suitable for treatment with Absorb were registered.

Clinical follow-up is scheduled at 30 days, 180 days, and at 1, 2, and 3 years.

### *8.4.3 Demographics*

The mean age was 61.12 ± 10.75 years and 74.3% (603/812) of the subjects were male. Regarding medical risk factors, 23.2% (188/812) of the subjects were tobacco users, 69.3% (563/812) had hypertension requiring medication, and 67.7% (550/812) had dyslipidemia requiring medication. There were 36.7% (276/752) of the subjects with family history of premature coronary artery disease, and 28.5% (230/807) with prior MI history. In addition, 26.5% (215/812) of the subjects were diabetic, with 24.1% (196/812) requiring medication.

### *8.4.4 Clinical Results for ABSORB EXTEND*

Data out to 1 year were available for all 812 subjects enrolled into ABSORB EXTEND (**Table 8.4.4-1**). The composite endpoints are presented using the protocol definition per WHO for MI and are based on hierarchical counts unless otherwise noted. The 1-year MACE and TLF composite rates for ABSORB EXTEND were both 5.0% (41/812).

**Table 8.4.4-1: Key Clinical Outcomes of ABSORB EXTEND (ITT Population) through 1 Year**

| | Absorb (N = 812) |
|---|---|
| **COMPOSITE EFFICACY AND SAFETY** | |
| TLF | 5.0% (41/812) |
| **EFFICACY** | |
| Ischemia-Driven TLR | 2.3% (19/812) |
| TLR, CABG | 0.2% (2/812) |
| TLR, PCI | 2.1% (17/812) |
| Ischemia-Driven TVR | 2.8% (23/812) |
| **SAFETY** | |
| All Death | 1.1% (9/812) |
| Cardiac Death | 0.7% (6/812) |
| Vascular Death | 0.1% (1/812) |
| Non-cardiovascular death | 0.2% (2/812) |
| TV-MI | 3.3% (27/812) |
| QMI | 1.0% (8/812) |
| NQMI | 2.3% (19/812) |
| All MI | 3.3% (27/812) |
| QMI | 1.0% (8/812) |
| NQMI | 2.3% (19/812) |
| **Cumulative ARC-defined Definite + Probable Stent / Scaffold Thrombosis (0-365 days)** | 1.0% (8/809) |
| Acute (< 1 day) | 0.0% (0/812) |
| Sub-Acute (1-30 days) | 0.6% (5/812) |
| Late (31-365 days) | 0.4% (3/807) |

**Note:** 1-year timeframe includes a window of ± 28 days
**Note:** N is the total number of subjects
**Note:** MI per protocol definition per WHO

## 8.5 ABSORB II Randomized Clinical Trial

The ABSORB II Randomized Clinical Trial RCT (ABSORB II) is the first randomized controlled trial comparing Absorb to XIENCE.

### *8.5.1 Primary Objective*

The ABSORB II is a post-approval randomized clinical trial designed to compare the safety, efficacy and performance of Absorb compared to the XIENCE in the treatment of *de novo* native coronary artery lesions.

### *8.5.2 Design*

The ABSORB II is a prospective, randomized (2:1 Absorb to XIENCE), active-controlled, single-blinded, multicenter clinical trial (Europe and New Zealand) registering 501 subjects. Target lesions were up to two *de novo* native coronary artery lesions, each located in different major epicardial vessels, all with an angiographic maximal luminal diameter between 2.25 mm and 3.8 mm as estimated by on-line quantitative coronary angiography (QCA), and a lesion length of ≤ 48 mm. Planned overlapping of study devices are allowed for treatment of long lesions.

The co-primary endpoints of the study are vasomotor function assessed by change in mean lumen diameter between pre- and post-nitrate at 3 years (superiority) and minimum lumen diameter changes from post-procedure to 3 years (non-inferiority, reflex to superiority), both by angiography. Vasomotor function is tested for superiority using a t-test at two-sided alpha of 0.05. Minimum Lumen Diameter change is tested for non-inferiority (non-inferiority margin of 0.14 mm) using an asymptotic test at one-sided alpha of 0.05. If non-inferiority is met with higher value in the Absorb arm, then superiority will be tested using a t-test at two-sided alpha of 0.05. Analyses of secondary endpoints are descriptive.

### *8.5.3 Demographics*

The mean age was 61.5 ± 10.0 and 60.9 ± 10.0 years in the Absorb and XIENCE arms, respectively. The patient population was predominantly male (75.5% in the Absorb arm and 79.5% in the XIENCE arm). In the study population, there was high prevalence of comorbidities of hypertension (69.0% vs. 71.7% for Absorb and XIENCE arms, respectively) and dyslipidemia (75.2% vs. 80.1% for Absorb and XIENCE arms, respectively). Over 20% of the population was diabetic (23.9% vs. 24.1% for Absorb and XIENCE arms, respectively). The proportion of patients with triple (or more) of diseased, native, major epicardial coronary arteries were 2.4% (8/335) in the Absorb arm and 3.6% (6/166) in the XIENCE arm.

### *8.5.4 Results*

The 1-year safety and efficacy results are presented in **Table 8.5.4-1**. These analyses are based on the ITT population. The TLF rate at 1 year was 4.8% in the Absorb arm and 3.0% in the XIENCE arm; there was no statistical difference. There was no statistical difference in scaffold / stent thrombosis rate between Absorb and XIENCE.

**Table 8.5.4-1: ABSORB II Clinical Results (ITT population) through 1 Year**

| | Absorb (N = 335) | XIENCE (N = 166) | Difference [95% CI][1] |
|---|---|---|---|
| **COMPOSITE EFFICACY AND SAFETY** | | | |
| TLF | 4.8% (16/331) | 3.0% (5/165) | 1.80% [-2.48%, 5.16%] |
| **EFFICACY** | | | |
| Ischemia-Driven TLR | 1.2% (4/331) | 1.8% (3/165) | -0.61% [-4.08%, 1.60%] |
| TLR, CABG | 0.0% (0/331) | 0.0% (0/165) | 0.00% [N/A] |
| TLR, PCI | 1.2% (4/331) | 1.8% (3/165) | -0.61% [-4.08%, 1.60%] |
| Ischemia-Driven TVR | 1.8% (6/331) | 3.6% (6/165) | -1.82% [-6.01%, 1.04%] |
| **SAFETY** | | | |
| All Death | 0.0% (0/331) | 0.6% (1/165) | -0.61% [-3.35%, 0.65%] |
| Cardiac Death | 0.0% (0/331) | 0.0% (0/165) | 0.00% [N/A] |
| Vascular Death | 0.0% (0/331) | 0.0% (0/165) | 0.00% [N/A] |
| Non-cardiovascular Death | 0.0% (0/331) | 0.6% (1/165) | -0.61% [-3.35%, 0.65%] |
| TV-MI | 4.2% (14/331) | 1.2% (2/165) | 3.02% [-0.51%, 5.90%] |
| QMI | 0.6% (2/331) | 0.0% (0/165) | 0.60% [-1.71%, 2.18%] |
| NQMI | 3.6% (12/331) | 1.2% (2/165) | 2.41% [-1.05%, 5.16%] |
| All MI | 4.5% (15/331) | 1.2% (2/165) | 3.32% [-0.25%, 6.26%] |
| QMI | 0.6% (2/331) | 0.0% (0/165) | 0.60% [-1.71%, 2.18%] |
| NQMI | 3.9% (13/331) | 1.2% (2/165) | 2.72% [-0.78%, 5.53%] |
| Cardiac Death or MI | 4.5% (15/331) | 1.2% (2/165) | 3.32% [-0.25%, 6.26%] |
| **Cumulative ARC-defined Definite + Probable Stent / Scaffold Thrombosis (0-393 days)** | 0.9% (3/329) | 0.0% (0/164) | 0.91% [-1.45%, 2.65%] |
| Acute (≤ 1 day) | 0.3% (1/335) | 0.0% (0/166) | 0.30% [-1.98%, 1.67%] |
| Sub-Acute (> 1-30 days) | 0.3% (1/334) | 0.0% (0/166) | 0.30% [-1.98%, 1.68%] |
| Late (31-365 days) | 0.3% (1/329) | 0.0% (0/164) | 0.30% [-2.00%, 1.70%] |
| Very Late (> 365-393 days) | 0.0% (0/329) | 0.0% (0/164) | 0.00% [N/A] |

[1] By Newcombe score method
**Note:** 1-year timeframe includes a window of ± 28 days
**Note:** N is the total number of subjects
**Note:** MI is per protocol definition

## 8.6 ABSORB Japan Randomized Controlled Trial

The ABSORB Japan Randomized Controlled Trial (ABSORB Japan) is the pivotal trial to support the Japan approval of Absorb. The ABSORB Japan has completed its enrollment and registration and follow-up are ongoing.

### *8.6.1 Primary Objective*

To evaluate the safety and effectiveness of Absorb in the treatment of subjects with ischemic heart disease caused by *de novo* native coronary artery lesions in Japanese population by

comparing with approved metallic drug eluting stent (XIENCE).

### *8.6.2 Design*

The ABSORB Japan is a prospective, randomized (2:1 Absorb to XIENCE), active-controlled, single-blinded, multicenter clinical trial in Japan registering 400 subjects. Treatment of up to two *de novo* native coronary artery lesions, each lesion located in different major epicardial vessels, was allowed. The maximum diameter ($D_{max}$), by quantitative methods, was required to be ≥ 2.5 mm and ≤ 3.75 mm and lesion length of ≤ 24 mm, by visual estimation. Treatment of one non-target lesion with XIENCE in addition to one target lesion, per assignment, was allowed.

Absorb was available in diameters of 2.5, 3.0, and 3.5 mm and lengths of 8, 12, 18 and 28 mm (8 mm not available for 3.5 mm diameter). All commercial sizes and diameters of XIENCE were available except for the 2.25 mm diameter and the 33 and 38 mm lengths. Overlap with same device as assigned, was allowed in the case of bailout.

The primary endpoint of the study is TLF (composite of cardiac death, myocardial infarction attributable to target vessel, or ischemia-driven target lesion revascularization) at 1 year, non-inferiority against the control. The primary endpoint is evaluated using the difference in event rates in the ITT population. The hypothesis test is designed to show non-inferiority of Absorb to XIENCE.

Powered secondary endpoints are the in-segment late loss at 13 months by angiography (non-inferiority), the in-device mean lumen area change, from post-procedure to 3 years by IVUS (superiority) and the in-device mean lumen diameter change, between pre- and post-nitrate infusion at 3 years by angiography (superiority).

Clinical follow-up is planned at 30 days, 180 days, and at 1, 2, 3, 4 and 5 years. All subjects undergo coronary angiography pre- and post-procedure, at 13 months and at 3 years. In addition, a subgroup of 120 subjects will undergo evaluation of vaso-reactivity induced by acetylcholine (ACh) at 4 years.

Following the index procedure, all subjects must be maintained on an IFU-specified dose of ADP antagonist for a minimum of 12 months, and aspirin (80 mg) for an indefinite period.

### *8.6.3 Demographics*

The population of the ABSORB Japan clinical trial was predominantly male (78.9% in the Absorb arm, 73.9% in the XIENCE arm). The mean age was 67.1 ± 9.4 years in the Absorb arm and 67.3 ± 9.6 years in the XIENCE arm. In the study population, there was a high prevalence of comorbidities of hypertension (78.2% vs. 79.9% for Absorb and XIENCE arms, respectively) and dyslipidemia (82.0% vs. 82.1% for Absorb and XIENCE arms, respectively). Over 30% of the population was diabetic (36.1% vs. 35.8% for Absorb and XIENCE arms, respectively). The proportion of patients with two (or more) lesions treated were 10.9% (29/266) in the Absorb arm and 9.7% (13/134) in the XIENCE arm.

### *8.6.4 Results*

The safety and efficacy results for the ABSORB Japan trial are presented in **Table 8.6.4-1**. The Absorb arm was non-inferior to XIENCE with a non-inferiority p-value of < 0.0001 for TLF rates at 1 year. The TLF rate at 1 year was 3.8% (5/133) in the XIENCE arm and 4.2% (11/265) in the Absorb arm. Absorb and XIENCE were not statistically different in the safety and efficacy endpoints. Scaffold / stent thrombosis rates were the same at 1 year for both Absorb and

XIENCE.

**Table 8.6.4-1: ABSORB Japan Clinical Results through 1 Year (ITT Population)**

| | Absorb (N = 266) | XIENCE (N = 134) | Difference [95% CI][1] |
|---|---|---|---|
| **COMPOSITE EFFICACY AND SAFETY** | | | |
| TLF | 4.2% (11/265) | 3.8% (5/133) | 0.39% [-4.68%, 4.18%] |
| **EFFICACY** | | | |
| Ischemia-Driven TLR | 2.6% (7/265) | 2.3% (3/133) | 0.39% [-4.00%, 3.48%] |
| TLR, CABG | 0.0% (0/265) | 0.0% (0/133) | 0.00% [-2.81%, 1.43%] |
| TLR, PCI | 2.6% (7/265) | 2.3% (3/133) | 0.39% [-4.00%, 3.48%] |
| Ischemia-Driven TVR | 4.9% (13/265) | 3.8% (5/133) | 1.15% [-4.00%, 5.09%] |
| **SAFETY** | | | |
| All Death | 0.8% (2/265) | 0.0% (0/133) | 0.75% [-2.11%, 2.71%] |
| Cardiac Death | 0.0% (0/265) | 0.0% (0/133) | 0.00% [-2.81%, 1.43%] |
| Vascular Death | 0.4% (1/265) | 0.0% (0/133) | 0.38% [-2.45%, 2.11%] |
| Non-cardiovascular Death | 0.4% (1/265) | 0.0% (0/133) | 0.38% [-2.45%, 2.11%] |
| TV-MI | 3.4% (9/265) | 2.3% (3/133) | 1.14% [-3.32%, 4.43%] |
| QMI | 1.1% (3/265) | 0.0% (0/133) | 1.13% [-1.77%, 3.27%] |
| NQMI | 2.3% (6/265) | 2.3% (3/133) | 0.01% [-4.33%, 2.99%] |
| All MI | 3.4% (9/265) | 2.3% (3/133) | 1.14% [-3.32%, 4.43%] |
| QMI | 1.1% (3/265) | 0.0% (0/133) | 1.13% [-1.77%, 3.27%] |
| NQMI | 2.3% (6/265) | 2.3% (3/133) | 0.01% [-4.33%, 2.99%] |
| Cardiac Death or MI | 3.4% (9/265) | 2.3% (3/133) | 1.14% [-3.32%, 4.43%] |
| **Cumulative ARC-defined Definite + Probable Stent / Scaffold Thrombosis (0-365 days)** | 1.5% (4/262) | 1.5% (2/133) | 0.02% [-3.90%, 2.60%] |
| Acute (≤ 1 day) | 0.0% (0/266) | 0.0% (0/133) | 0.00% [-2.81%, 1.42%] |
| Sub-Acute (> 1-30 days) | 1.1% (3/265) | 0.8% (1/133) | 0.38% [-3.09%, 2.61%] |
| Late (31-365 days) | 0.4% (1/262) | 0.8% (1/133) | -0.37% [-3.77%, 1.48%] |

[1] By Newcombe score method
**Note:** 1-year timeframe includes a window of ± 28 days
**Note:** N is the total number of subjects
**Note:** MI is per protocol definition

## 8.7 Benefits of the Absorb GT1 Bioresorbable Scaffold Technology

The ABSORB III clinical trial builds upon the clinical evidence of the ABSORB family of trials (ABSORB Cohort B, ABSORB EXTEND, ABSORB II, and ABSORB Japan). Collectively, these clinical studies support the safety and effectiveness of Absorb. In the ABSORB Cohort B clinical investigation, Absorb showed excellent long-term clinical outcomes with low MACE rates out to 5 years with absence of cardiac death, Q wave MI and scaffold thrombosis. In addition, Absorb demonstrated good patency out to 5 years. Additionally, one-year ABSORB II, ABSORB EXTEND, and ABSORB Japan clinical outcome data again demonstrated and confirmed the safety and performance of the Absorb with comparable TLF, revascularization (ID-TLR), and stent / scaffold thrombosis rates as the commercially available XIENCE stent.

Absorb thus performs all the functions of a drug-eluting stent while offering future potential benefits resulting from the absence of a permanent implant. The gradual disappearance of the scaffold allows for the possibility of vascular healing and restoration of vessel function as discussed in the Vasomotor Function Results at 2, 3 and 5 Years (**Section 8.3.8 - ABSORB Cohort B, Vasomotor Function Outcomes**). The absence of a permanent implant in the vascular tissue may facilitate any required re-interventions on the target vessel / lesion or side branches either by percutaneous or surgical means, thus enabling a broader range of treatment options after bioresorption of the scaffold.

Finally, unlike permanent metal implants, polymeric implants do not cause imaging artifacts during non-invasive CT or MR evaluation. This provides the additional benefit that a polymeric bioresorbable scaffold may be more compatible with the growing usage of non-invasive follow-up imaging than is the case with metallic stents, potentially facilitating patient management and providing economic benefits.

# 9.0 PATIENT SELECTION AND TREATMENT

## 9.1 Individualization of Treatment

The risks and benefits described above should be considered for each patient before using the Absorb GT1 BVS System. Patient selection factors to be assessed should include judgment regarding risk of antiplatelet therapy. Special consideration should be given to those patients with recently active gastritis or peptic ulcer disease.

Antiplatelet drugs should be used in combination with the Absorb GT1 BVS per ACC / AHA and ESC guidelines. Physicians should use the information from the ABSORB family of clinical trials, coupled with the current literature on drug-eluting stents / scaffolds and the specific needs of individual patients, to determine the specific antiplatelet / anticoagulation dose and duration to be used for their patients in general practice. In ABSORB III, all patients were to be maintained on 75 mg of clopidogrel daily or 5 or 10 mg of prasugrel daily (10 mg preferred in most patients) or 90 mg twice daily of ticagrelor for a minimum of 12 months, and ≥ 75 mg of aspirin daily for the length of the clinical investigation.

It is very important that the patient comply with the post-procedural antiplatelet recommendations. Premature discontinuation of prescribed antiplatelet medication could result in a higher risk of thrombosis, myocardial infarction (MI), or death. Prior to PCI, if a surgical or dental procedure is anticipated that requires early discontinuation or temporary interruption of

antiplatelet therapy, the interventionalist and patient should carefully consider whether an everolimus-eluting scaffold and its associated recommended antiplatelet therapy are the appropriate PCI choice. Following PCI, should a surgical or dental procedure be recommended, the risks and benefits of the procedure should be weighed against the possible risk associated with premature or temporary discontinuation of antiplatelet therapy.

Patients who require premature discontinuation of antiplatelet therapy secondary to significant active bleeding, should be monitored carefully for cardiac events, and once stabilized, have their antiplatelet therapy restarted as soon as possible per the discretion of their treating physicians.

## 10.0 PATIENT COUNSELING AND PATIENT INFORMATION

Similar to metallic stents, physicians should consider the following in counseling patients about this product:

- Discuss the risks associated with scaffold placement
- Discuss the risks associated with an everolimus eluting bioresorbable vascular scaffold
- Discuss the risks of early discontinuation of the antiplatelet therapy
- Discuss the risks of late thrombosis with scaffold use in higher risk patient subgroups
- Discuss the risk / benefit issues for this particular patient
- Discuss alternation to current life style immediately following the procedure and over the long term

The following patient materials are provided for this product:

- A Patient Information Guide, including information on coronary artery disease, the implant procedure and the Absorb GT1 BVS System (provided to physician, on-line at http://www.abbottvascular.com, or by calling customer service 1-800-227-9902).
- A Scaffold Implant Card, including both patient information and scaffold implant information (provided in package).

## 11.0 HOW SUPPLIED

**Sterile** – This device is E-beam radiation-sterilized. Non-pyrogenic. Do not use if the package is open or damaged.

This single-use device cannot be reused on another patient, as it is not designed to perform as intended after the first usage. Changes in mechanical, physical, and / or chemical characteristics introduced under conditions of repeated use, cleaning, and / or resterilization may compromise the integrity of the design and / or materials, leading to contamination due to narrow gaps and / or spaces and diminished safety and / or performance of the device. Absence of original labeling may lead to misuse and eliminate traceability. Absence of original packaging may lead to device damage, loss of sterility, and risk of injury to the patient and / or user.

**Contents –** One (1) Absorb GT1 Bioresorbable Vascular Scaffold (BVS) System; one (1) temperature monitor

**Storage –** Store at or below 25°C (77°F); excursions permitted to 30°C (86°F)

## 12.0 CLINICIAN USE INFORMATION

### 12.1 Inspection Prior to Use

Prior to using the Absorb GT1 BVS System, carefully remove the system from the package and inspect for bends, kinks and other damage. Verify that the scaffold does not extend beyond the radiopaque balloon markers and that it is still well-crimped onto the balloon catheter. Do not use if any defects are noted.

### 12.2 Materials Required

- Appropriate arterial sheath
- 2–3 syringes (10–20 cc)
- 1,000 u/500 cc heparinized normal saline (HepNS)
- 6F / 0.070" / 1.8 mm minimum inner diameter guiding catheter(s) of appropriate shape for the target vessel
- Rotating hemostatic valve with 0.096 inch (2.44 mm) minimum inner diameter
- 0.014 inch (0.36 mm) x 175 cm (minimum length) guide wire
- Torque device
- Guide wire introducer
- Contrast diluted 1:1 with heparinized normal saline
- Appropriate sized pre-dilatation angioplasty balloon
- Appropriate sized post-dilatation noncompliant angioplasty balloon
- Inflation device
- Three-way stopcock
- Appropriate anticoagulation and antiplatelet drugs

### 12.3 Vessel and Lesion Selection

- **Quantitative imaging is strongly recommended** for the assessment of target vessel diameter at baseline for appropriate Absorb GT1 BVS size selection.

- The target vessel diameter ranges to be treated in the procedure are indicated in **Table 12.3-1**, along with the Absorb GT1 BVS diameter to be used.

**Table 12.3-1: Target Vessel Diameter Ranges and Absorb GT1 BVS Diameter to be Used (Quantitative Imaging)**

| Target Vessel Diameter Distal and Proximal | Absorb GT1 BVS Diameter to be Used |
|---|---|
| ≥ 2.5 mm and < 2.75 mm | 2.5 mm |
| ≥ 2.75 mm and < 3.25 mm | 3.0 mm |
| ≥ 3.25 mm and ≤ 3.75 mm | 3.5 mm |

- **If visual estimation is used:**
    - **Use the pre-dilatation balloon, when inflated, to assist in sizing the vessel.**

- For cases where the combination of target vessel diameter and target lesion length is appropriate to be treated by more than one scaffold size, the selection of scaffold size can be made per the judgment of the physician.

## 12.4 Preparation

### *12.4.1 Packaging Removal*

**Note: The foil pouch is the sterile barrier. Sterile product is contained within this one pouch – there is no secondary pouch.**

- Peel the pouch open from the top corner.
- Carefully remove the delivery system from its protective tubing for preparation of the delivery system.
- Do not bend or kink the hypotube during removal.

### *12.4.2 Dual Layer Sheath Removal*

1. While holding the distal catheter shaft with one hand, grasp only the yellow outer sheath with the other hand and gently slide the sheath distally.
2. A longitudinal split on the inner sheath will open up and be visible.
3. The stylet and dual layer sheath are removed simultaneously from the delivery system by continuing to slide the yellow sheath distally until the inner and outer layers of the dual layer sheath as well as the stylet are free from the catheter system. See **Section 5.1 - Precautions, Scaffold Handling.** Do not use the device if the sheath cannot be removed as indicated.
4. Verify that the scaffold does not extend beyond the radiopaque balloon markers and no scaffold struts are lifted. **Do not use if any defects are noted.**

### *12.4.3 Guide Wire Lumen Flush*

1. Flush the guide wire lumen with HepNS until fluid exits the guide wire exit notch.
   **Note:** Avoid manipulation of the scaffold while flushing the guide wire lumen as this may disrupt the placement of the scaffold on the balloon.

### *12.4.4 Delivery System Preparation*

1. Prepare an inflation device / syringe with diluted contrast medium.
2. Attach an inflation device / syringe to stopcock; attach it to the inflation port of the product.
   Do not bend the product hypotube when connecting to the inflation device / syringe.
3. With the tip down, orient the delivery system vertically.
4. Open the stopcock to delivery system; pull negative for 30 seconds; release to neutral for contrast fill.
5. Close the stopcock to the delivery system; purge the inflation device / syringe of all air.
6. Repeat steps 3 through 5 until all air is expelled. If bubbles persist, do not use the product.
7. If a syringe was used, attach a prepared inflation device to the stopcock.
8. Open the stopcock to the delivery system.
9. Leave on neutral.

**Note:** The labeled scaffold diameter refers to expanded scaffold inner diameter.

## 12.5 Delivery Procedure

1. Prepare the vascular access site according to standard practice.
2. **Pre-dilate the lesion to match the reference vessel diameter with a percutaneous transluminal coronary angioplasty catheter.** Pre-dilatation should be performed with an angioplasty balloon which can also be utilized to properly size the vessel.

   **Note:** Limit the length of the pre-dilatation by the PTCA balloon to avoid creating a region of vessel injury that is outside the boundaries of the Absorb GT1 scaffold.
3. Administer a standard dose of intracoronary nitroglycerine prior to finalizing the RVD within the target zone.
4. Maintain neutral pressure on the inflation device. Open the rotating hemostatic valve as wide as possible.
5. Backload the delivery system onto the proximal portion of the guide wire, while maintaining guide wire position across the target lesion.
6. Advance the delivery system over the guide wire to the target lesion. Utilize radiopaque balloon markers to position the scaffold across the lesion; perform angiography to confirm scaffold position.

   **Note:** If removal of a scaffold system is required prior to deployment, ensure that the guide catheter is coaxially positioned relative to the scaffold delivery system and cautiously withdraw the scaffold delivery system into the guiding catheter. Should **unusual resistance** be felt **at any time** when withdrawing the scaffold into the guide catheter, the scaffold delivery system and the guide catheter should be **removed as a single unit**. This should be done under direct visualization with fluoroscopy.
7. Tighten the rotating hemostatic valve. The scaffold is now ready to be deployed.

### 12.6 Deployment Procedure

1. **CAUTION: Refer to product label for *in vitro* scaffold inner diameter, nominal pressure and RBP.**
2. Prior to deployment, reconfirm the correct position of the scaffold relative to the target lesion using the radiopaque balloon markers.
3. Deploy the scaffold slowly, by pressurizing delivery system **in 2-atm increments over 5 seconds**, until scaffold is completely expanded. Maintain pressure for 30 seconds. Fully expand the scaffold by inflating to nominal pressure at a minimum; accepted practice generally targets an initial deployment pressure that would achieve a scaffold inner ratio of about 1.1 times the reference vessel diameter.

   **CAUTION: Do not exceed the labeled rated burst pressure RBP of 16 atm (1621 kPa) or maximum deployment diameter of the scaffold.**
4. Fluoroscopic visualization during scaffold expansion should be used in order to properly judge the optimum scaffold diameter as compared to the proximal and distal native coronary artery diameters (reference vessel diameter). Optimal scaffold expansion and proper apposition require that the scaffold be in full contact with the arterial wall.
5. If necessary, the delivery system can be repressurized or further pressurized to ensure complete apposition of the scaffold to the artery wall.

   Fully cover the entire lesion and balloon-treated area (including dissections) with the Absorb GT1 scaffold, allowing for adequate scaffold coverage into healthy tissue proximal and distal to the lesion.
6. Deflate the balloon by pulling negative on the inflation device for 30 seconds. Confirm complete balloon deflation before attempting to move the delivery system. If unusual resistance is felt during scaffold delivery system withdrawal, pay particular attention to the guiding catheter position.

   **Note:** See **Section 12.8 - Clinician Use Information, Removal Procedure** for instruction on withdrawal of scaffold delivery system.
7. Confirm scaffold position and deployment using standard angiographic techniques. For optimal results, the entire stenosed arterial segment should be covered by the scaffold. Fluoroscopic visualization during scaffold expansion should be used in order to properly judge the optimum expanded scaffold diameter as compared to the proximal and distal coronary artery diameter(s). Optimal expansion requires that the scaffold be in full contact with the artery wall, which can be facilitated with the use of routine angiography and post-dilatation. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) can be used to confirm scaffold apposition to the artery wall.
8. **Post-dilatation is strongly recommended for optimal scaffold apposition.** When performed, follow the instructions in **Section 12.7 - Clinician Use Information, Further Expansion of the Deployed Scaffold**, as long as the post-dilated segment is within the allowable expansion limits of the scaffold.

### 12.7 Further Expansion of the Deployed Scaffold

1. **DEPLOYED SCAFFOLDS SHOULD NOT BE LEFT UNDER DILATED.**

   Deployed scaffolds should be well-apposed to the vessel wall. To achieve optimal scaffold apposition, post-dilatation is strongly recommended, especially for small vessels. When performed, post-dilatation should be at high pressure (> 16 atm) with a noncompliant balloon*.

   ***Note:** Limit choice of noncompliant balloon nominal diameter to be no more than 0.5 mm above the scaffold nominal diameter to stay within the scaffold's maximum expansion limit. **The compliance chart of the noncompliant balloon selected must be carefully reviewed prior to dilatation and an appropriate maximum pressure used to ensure that the scaffold is not over dilated.**

   The scaffolded segment should be carefully recrossed with a prolapsed guide wire to avoid disrupting the scaffold geometry. Post-dilatation must only be done with balloons sized to fit within the boundaries of the scaffold.

   **CAUTION: Do not dilate the scaffold beyond the dilatation limit which is 0.5 mm above the nominal diameter. Over-dilatation may result in scaffold damage.**

| Nominal Scaffold Diameter | Dilatation Limit |
|---|---|
| **2.5 mm** | **3.00 mm Maximum post-dilatation diameter** |
| **3.0 mm** | **3.50 mm Maximum post-dilatation diameter** |
| **3.5 mm** | **4.00 mm Maximum post-dilatation diameter** |

2. If more than one Absorb GT1 BVS is needed to cover the lesion and balloon-treated area, it is suggested that, to avoid the potential for gap restenosis, the scaffolds be overlapped by a minimum of 1 mm and a maximum of 4 mm. The least amount of overlap is recommended. To ensure that there are no gaps between scaffolds, the balloon marker bands of the second Absorb GT1 BVS should be positioned inside the deployed scaffold, just above the marker beads, prior to expansion. It is recommended not to use more than two Absorb GT1 BVS to treat one lesion.
3. Ensure the final scaffold diameter matches the reference vessel diameter to **ENSURE GOOD SCAFFOLD APPOSITION**. Reconfirm scaffold position and angiographic results. Repeat inflations until achieved.

### 12.8 Removal Procedure

**Withdrawal of the scaffold delivery catheter / post-dilatation balloon from the deployed scaffold:**

1. Deflate the balloon by pulling negative on the inflation device. Larger and longer balloons will take more time (up to 30 seconds) to deflate than smaller and shorter balloons. Confirm balloon deflation under fluoroscopy.
2. Position the inflation device to “negative” or “neutral” pressure.
3. Fully open the rotating hemostatic valve.
4. Stabilize guide catheter position just outside coronary ostium and anchor in place. Maintain guide wire placement across scaffolded segment.
5. Gently remove the scaffold delivery system with slow and steady pressure.
6. Tighten the rotating hemostatic valve.

**If, during withdrawal of the catheter from the deployed scaffold, resistance is encountered, use the following steps to improve balloon rewrap:**

- Re-inflate the balloon up to nominal pressure, deflate and change pressure to neutral.
- Repeat steps 1–5 above.
- Re-evaluate the scaffolded region once the balloon is removed to ensure optimal apposition.

**Note:** See **Section 5.4 - Precautions, Scaffold / System Removal** for specific delivery system removal instructions.

### 13.0 TRADEMARKS

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**Graphical Symbols for Medical Device Labeling**

| | | | | | |
|---|---|---|---|---|---|
| Manufacturer | REF Catalogue number | F French size | RX Rapid exchange | 30°C (86°F) EXCURSIONS Excursions permitted to temperature | Separate collection for waste electrical / electronic equipment |
| MANUFACTURED BY Manufactured by | Do not reuse | Do not resterilize | 25°C (77°F) Upper limit of temperature | MR MR Conditional MR Conditional | |
| Use by | Date of manufacture | LOT Batch code | | | Rx ONLY Caution: Federal (USA) Law restricts this device to sale by or on the order of a physician |
| Inner diameter | Outer diameter | STERILE R Sterilized using irradiation | Guiding catheter | | |
| Consult instructions for use | Contents (numeral represents quantity of units inside) | Caution: Consult instructions for use for warnings and precautions | Non-pyrogenic | Do not use if package is damaged | |