Rationale and design of the TAXUS Libertē Post-Approval Study: Examination of patients receiving the TAXUS Liberté stent with concomitant prasugrel therapy in routine interventional cardiology practice

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Background Observational studies of new coronary stents are necessary to assess performance in a variety of complex patient and lesion types. Furthermore, the optimal dose and duration of thienopyridine treatment is unclear, particularly in patients with complex clinical conditions. The TAXUS Libertē Post-Approval Study is designed to provide 5-year data on the TAXUS Liberté paclitaxel-eluting stent with concomitant prasugrel therapy in routine clinical practice and to contribute data to the DAPT study.

Study Design The TAXUS Libertē Post-Approval Study is a prospective, multicenter, observational study. Enrollment of approximately 4,200 patients receiving ≥1 TAXUS Liberté stents is planned. All patients without a contraindication will be prescribed prasugrel plus aspirin for 1 year. The 12-month primary end point of cardiac death or myocardial infarction in on-label stent patients will be compared with historical TAXUS Express stent data from the TAXUS ATLAS and TAXUS ARRIVE studies. Secondary clinical end points include stent thrombosis, all-cause death, stroke, revascularization, and bleeding in all patients. In addition, this study will be the first to evaluate prasugrel use in a routine practice setting (including 5 and 10 mg daily doses) and will contribute data to the DAPT Study, comparing 12 versus 30 months of dual antiplatelet therapy after drug-eluting stent placement.

Summary The TAXUS Libertē Post-Approval Study will be the first to provide long-term real-world data on use of the TAXUS Liberté Stent with prasugrel treatment. The study is currently enrolling, and primary end point data are expected in mid 2013. (Am Heart J 2012;163:142-148.e6.)

Background and rationale

Pivotal randomized clinical trials have demonstrated consistent reductions in restenosis with the use of drug-eluting coronary stents (DESs) compared with bare-metal stents (BMSs).[1,2] However, because of the need for a homogenous population, pivotal studies restrict stent use to well-defined patients and clinical settings and simple lesion types. Approximately 60% to 70% of DES is used in patients with more complicated clinical settings and coronary lesions than what has been represented in pivotal randomized DES trials.[3,4] Postapproval studies have proven to be important sources of information about "real-world" DES usage patterns and outcomes and also provide valuable information regarding long-term performance of new stent products.[3,4]

Although the efficacy and safety of DES versus BMS have been established,[1,2] early studies suggested a small but nonsignificant increase in very late stent thrombosis (ST)[5] after DES implantation. Current guidelines recommend clopidogrel or prasugrel for at least 12 months after DES placement.[6] However, the guidelines also state that earlier discontinuation should be considered if the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy. Thus, given the risk of bleeding,[7,8] the optimal period of antiplatelet therapy is unclear nor is it known whether patients with

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high-risk coronary lesions and conditions might benefit from a different period of antiplatelet treatment. The Harvard Clinical Research Institute DAPT study, a large-scale clinical study assessing the risks and benefits of dual antiplatelet therapy beyond 1 year, is designed to answer these questions, with participation from all United States DES manufacturers.[9]

Prasugrel is a thienopyridine antiplatelet compound with greater and more consistent inhibition of platelet aggregation than clopidogrel.[10] In the pivotal TRITON TIMI 38 study,[8] patients undergoing percutaneous coronary intervention (PCI) associated with an acute coronary syndrome and randomized to receive prasugrel had a significant reduction in the primary composite end point of cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal stroke at a median follow-up of 14.5 months compared with patients randomized to receive clopidogrel. Although prasugrel was also associated with an increase in major bleeding, the overall risk-benefit ratio favored prasugrel, and it was granted Food and Drug Administration (FDA) approval in July 2009. Like clopidogrel, prasugrel has been recommended for at least 12 months after DES implantation in patients not at high risk of bleeding.[6] However, based on the reduced efficacy and increased risk of bleeding in certain subsets in the TRITON TIMI 38 trial (those weighing <60 kg or those ≥75 years old),[8] the FDA has recommended consideration of a lower maintenance dose of prasugrel (5 mg) in patients <60 kg and that prasugrel be considered in those ≥75 years old only in the presence of higher clinical risk (eg, diabetes or MI).[11]

Therefore, the prospective, multicenter TAXUS Libertē Post-Approval Study was designed to (1) provide FDA-mandated 5-year data on the use of the TAXUS Liberté paclitaxel-eluting stent in routine clinical practice, including cardiac death, MI, ST, all-cause death, stroke, revascularization, and bleeding in both on- and off-label stented patients; (2) provide necessary long-term information on the utility of prasugrel in a broad spectrum of stent recipients; (3) test a recommended lower 5-mg maintenance dose of prasugrel in patients ≥75 years old or <60 kg in weight, as in the TRILOGY ACS[12] trial; and (4) contribute data to the randomized DAPT study to assess the optimal duration of dual antiplatelet therapy. The unique characteristics of the TAXUS Libertē Post-Approval Study design and analysis plan are described herein.

Methods/design

Study device and study drug

The TAXUS Liberté paclitaxel-eluting stent (Boston Scientific Corporation, Natick, MA) consists of a balloon-expandable 316-L stainless steel stent coated with the Translute polymer containing paclitaxel in a dose density of 1 μg/mm^2.[2] Prasugrel (Eli Lilly & Company, Indianapolis, IN, and Daiichi Sankyo, Inc, Edison, NJ) is a third-generation oral, irreversible, thienopyridine inhibitor of the platelet $P2Y_{12}$ adenosine diphosphate receptor.[10,13] Prasugrel is indicated in the United States to reduce thrombotic cardiovascular events (including ST) in patients with acute coronary syndrome who are to be managed with PCI.[11] Prasugrel treatment is initiated as a single 60-mg loading dose and then continued orally at 10 mg once daily. Based on US labeling, for patients <60 kg in body weight, a 5 mg once daily maintenance dose is recommended,[11] although the effectiveness and safety of this dose have not been studied prospectively. As noted earlier, in the TAXUS Libertē trial, as in the TRILOGY ACS trial, the lower 5-mg maintenance dose will also be permitted in those ≥75 years old.

TAXUS Libertē Post-Approval Study design and population

The TAXUS Libertē Post-Approval Study is a prospective, multicenter study designed to collect safety and clinical outcomes data for patients receiving ≥1 TAXUS Liberté stents and prasugrel as the thienopyridine component of dual antiplatelet therapy. Approximately 4,200 patients are planned for enrollment. Patients with ischemic heart disease due to stenotic lesions in either native coronary arteries or coronary artery bypass grafts and no contraindications to prolonged dual antiplatelet therapy with prasugrel plus aspirin are eligible. Additional inclusion and exclusion criteria are given in Online Appendix A. These criteria assure that all patients enrolled in the TAXUS Libertē Post-Approval Study will also be eligible for participation in the randomized DAPT study (Online Appendix B), although not all TAXUS Libertē Post-Approval Study patients are expected to participate in the DAPT study. Participating physicians at up to 100 US study centers may each enroll up to 250 consented patients receiving a TAXUS Liberté stent.

To ensure a large enough sample of patients with on-label stent indications for the prespecified statistical analyses (see "Primary end point" section below), after initial enrollment of 3,600 patients, only on-label patients will be enrolled. On-label for the purposes of the study analyses excludes patients with the following baseline or target lesion characteristics: acute MI (AMI), cardiogenic shock, renal disease (serum creatinine >3.0 mg/dL or dialysis), bifurcation, chronic total occlusion, prior brachytherapy, graft stenting, in-stent restenosis, left main coronary disease or stenting, large vessel (reference vessel diameter [RVD] >3.75 mm), small vessel (RVD <2.5 mm), long lesion (>28 mm), moderate/severe calcification, multivessel stenting, ostial lesion, or severe tortuosity.[3] Enrollment is planned to continue until at least 1,675 on-label patients and at least 470 on-label medically treated diabetic patients (defined as treatment with oral hypoglycemic agents or insulin at enrollment) are enrolled, reaching approximately 4,200 total patients. It was originally estimated that 40% of the total enrolled population would consist of on-label stent patients; the protocol was amended based on the actual number (~30%) and approved by FDA.

All patients receiving a TAXUS Liberté stent will be prescribed aspirin and either 10 (recommended for patients <75 years old or ≥60 kg in weight) or 5 mg (recommended for patients ≥75 years old or <60 kg in weight) of daily open-label prasugrel for the first 12 months (Table I). Thienopyridine treatment

Table I. TAXUS Libertē Post-Approval Study aspirin and prasugrel recommended doses

Aspirin and thienopyridine loading dose
75 mg/d of aspirin for at least 3 d before the start of the index procedure or a periprocedural loading dose of 250-500 mg
60 mg periprocedural loading dose of prasugrel, if required
Patient with a periprocedural loading dose of thienopyridine other than prasugrel may be enrolled provided that switch to prasugrel occurs before discharge of the index hospitalization
Patient may switch from a thienopyridine other than prasugrel to prasugrel until discharge of the index hospitalization
Selection of aspirin and prasugrel maintenance dose
Recommended prasugrel maintenance dose
<75 y old and ≥60 kg in weight should receive a daily maintenance dose of 10-mg prasugrel
<60 kg in weight should receive a daily maintenance dose of 5-mg prasugrel
≥75-y-old is generally not recommended to receive prasugrel except in high-risk situations (such as diabetes or prior MI) where its effects appear to be greater and its use may be considered[11]
If prescribed in patients ≥75 y old, 5 mg maintenance dose should be used
If prasugrel maintenance dose is switched within 6 m before randomization, the patient will not be eligible for randomization*
Recommended aspirin maintenance dose
Daily dose of aspirin administered concomitantly with open-label prasugrel and/or study drug then continued indefinitely
75-325 mg aspirin daily for the first 6 m postindex procedure
75-162 mg beyond 6 m postindex procedure

*The patient will remain enrolled in the study and will be followed up through 5-year postindex procedure.

may be initiated with prasugrel, or, for patients who have received clopidogrel, therapy may be switched directly to prasugrel during the index hospitalization by replacing maintenance-dose clopidogrel with maintenance-dose prasugrel.[8] Follow-up will occur at 6, 12, 15, 18, 24, 30, and 33 months and then annually through 5-year postindex stent implantation.

All patients without contraindication will be prescribed aspirin indefinitely and prasugrel for 12 months. After the 12-month open-label period, eligible patients may be randomized to either continuing prasugrel for an additional 18 months or to placebo (Figure 1), with data being contributed to the ongoing DAPT study.[9] Key randomization inclusion criteria include patient compliance with prasugrel treatment (defined as no interruptions >14 consecutive days and patient-reported compliance between 80% and 120%) and an absence of major events (defined as all-cause death, MI, stroke, repeat coronary revascularization, ST, and global use of strategies to open occluded coronary arteries [GUSTO] severe or moderate major bleeding[14] [Online Appendix B]). Patients experiencing a repeat PCI, MI, or ST within the first 6 weeks of the index procedure may be included in the randomization, but patients experiencing major bleeding events, stroke, or coronary artery bypass graft within 6 weeks of the index procedure are excluded from randomization.

Randomization-eligible patients will be classified as either "complex" or "noncomplex" at the 12-month milestone, and randomization will be stratified by complexity and clinical site. Complex patients are considered to be at higher risk of late major adverse cardiac and cerebrovascular events (MACCE), which is defined as cardiac death, MI, target vessel revascularization (TVR), stroke, or ST. Patient and lesion factors constituting the "complex" classification have been previously defined.[9] After the 18-month randomized treatment period, all patients will be prescribed aspirin only for 3 months, followed by antiplatelet treatment of choice (at the physician's discretion) for the remainder of the 5-year follow-up period (Figure 1).

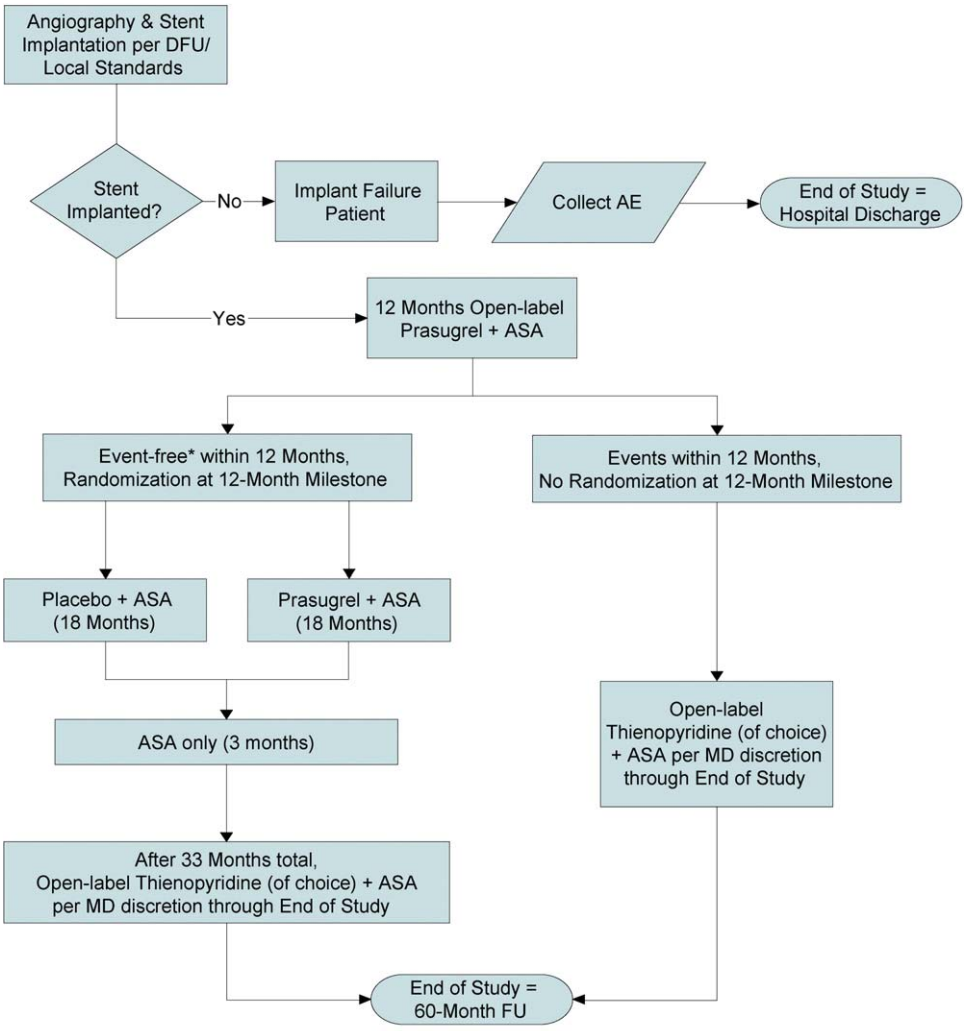
The TAXUS Libertē Post-Approval Study will follow up all patients for 5 years to evaluate device performance, regardless of whether the data contribute to the DAPT study. Although the TAXUS Libertē Post-Approval Study is not powered for comparisons of evaluating the impact of varying the length of dual antiplatelet therapy, the larger DAPT study is designed to address specific questions regarding optimal length of dual antiplatelet therapy.[9]

Statistics

The sample size was calculated to provide at least 80% power to test each of 3 objectives: the primary end point (cardiac death or MI rate in on-label patients), the secondary end point (annual increase in ST rate in on-label patients), and the diabetic subanalysis (target vessel failure [TVF] rate in on-label medically treated diabetic patients). The on-label sample size of approximately 1,675 patients is dependent upon the secondary end point for annual incremental ST rate in on-label patients.

Enrolled patients receiving at least 1 TAXUS Liberté stent in a target lesion will be included in the analysis sample. Simple descriptive statistics, graphs, and patient listings will be used to summarize most data. Treatment groups will be compared with the Student *t* test for continuous measures and a χ^2 or Fisher exact test for discrete variables. The Kaplan-Meier product-limit method will be used to estimate event or event-free rates for time-to-event outcomes, and treatment groups will be compared using log-rank and Wilcoxon tests. All comparisons and statistical tests of hypotheses, other than those prespecified for the primary end point, secondary end points, and prespecified subsets, will be for exploratory purposes only. Subsets of at least 200 enrolled patients will be considered for analysis, including off-label patients, patients treated with 10 or 5 mg prasugrel maintenance doses, and lesions in the setting of ST-elevation MI. Additional possible subset analyses are given in Online Appendix C. All statistical analyses will be

Figure 1



TAXUS Libertē Post Approval Study schematic. Patients free from death, MI, stroke, repeat revascularization, or GUSTO severe or moderate bleeding are eligible for randomization at 12 months. ASA indicates acetylsalicylic acid (aspirin); AE, adverse event; DFU, directions for use; FU, follow-up.

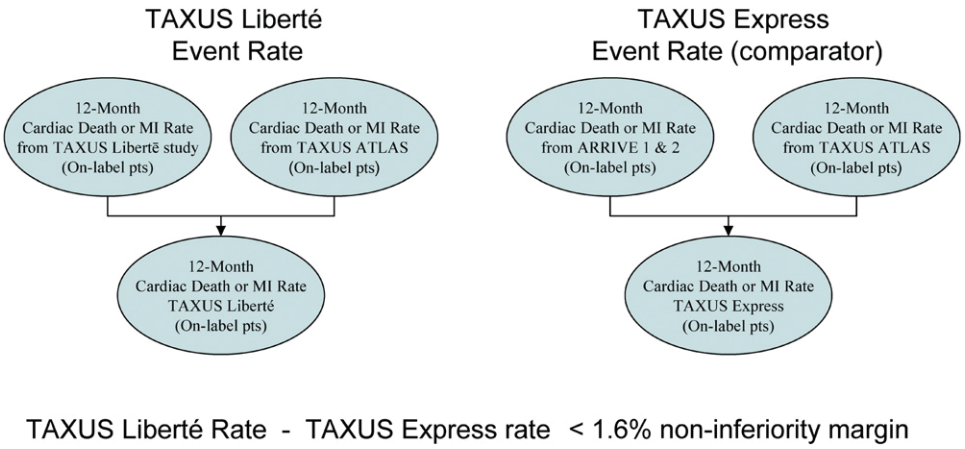
performed using SAS System Software, version 8 or above (SAS Institute, Cary, NC).

Primary end point

The primary end point for the TAXUS Libertē Post-Approval Study is the rate of cardiac death or MI (historical TAXUS definition; see Online Appendix D) through 12 months in on-label patients (per historical stent definition[2,3]). The 12-month cardiac death or MI rates in on-label TAXUS Liberté–treated patients from the TAXUS Libertē Post-Approval Study and the TAXUS ATLAS pivotal clinical trial[15] will be compared with on-label TAXUS Express–treated patients from the TAXUS ARRIVE 1 and 2 registries[3] and the historical control arm of the TAXUS ATLAS clinical trial (Figure 2[15]). A 1-sided z test (or χ^2 test) will be performed to determine if the cardiac death or MI rate for the TAXUS Liberté stent is noninferior to the cardiac death or MI rate for the TAXUS Express stent, assuming a prespecified noninferiority margin of 1.6% (Figure 2).

The 12-month cardiac death or MI rate is estimated to be 3.0% for TAXUS Express (the actual rate from pooled TAXUS Express–treated patients in TAXUS ATLAS[15] and ARRIVE[3]) and 3.4% for TAXUS Liberté (derived as the TAXUS Express rate plus a 0.4% estimated MI elevation due to a protocol-mandated postprocedural enzyme draw for medically treated diabetic patients in the TAXUS Libertē Post-Approval Study). Given a noninferiority

Figure 2



Primary end point. Noninferiority test of 12-month cardiac death or MI rate between on-label patients (per historic stent definition) receiving TAXUS Liberté versus TAXUS Express stents.

margin of 1.6% and a 1-sided 5% significance level, 2,363 on-label TAXUS Liberté patients will be required to provide 80% power. This will consist of 851 TAXUS Liberté patients from the TAXUS ATLAS trial[15] and at least 1,512 TAXUS Liberté on-label patients from TAXUS Libertē with 12-month follow-up. The control population (TAXUS Express) consists of 3,580 patients from the TAXUS ATLAS trial control arm and the on-label pooled TAXUS ARRIVE 1 and 2 populations through 12 months.[3,15] Propensity score subclassification method will be used to adjust baseline imbalance; potential covariates are prespecified in Online Appendix E.

Secondary end points

Using both historical TAXUS[2] and Academic Research Consortium (ARC)[16] definitions (Online Appendix D), the ST rate in the on-label TAXUS Liberté population will be analyzed. Other secondary clinical end points include all-cause death, stroke, TVR, and bleeding at each follow-up period (Table II). Additional analyses will be based upon the data at ≤24 hours, 30 days, 6 months, 12 months, 15 months, 24 months, 30 months, 33 months, and then annually through 5-year postindex stent implantation.

The on-label sample size of the TAXUS Libertē Post-Approval Study is determined from the expected annual incremental ST rate for on-label patients through 5 years after 1-year postindex procedure. The expected annual increase in the ST rate for TAXUS Liberté is estimated to be 0.5% based on the data available from the TAXUS Express pooled analysis.[2,17] The performance goal of 1.0% (expected rate + margin = 0.5% + 0.5%) was derived based on the upper confidence limit of <1.0% for each annual increment in the ST rate. Given a 1-sided 5% significance level, a minimum of 2,100 on-label TAXUS Liberté stent patients followed up through 5-year post stent index procedure will be required to provide at least 80% power. Allowing for an attrition rate of 17.5%, 2,546 TAXUS Liberté on-label patients will be required to achieve 2,100 patients with full 5-year follow-up. This will include 871 patients enrolled in TAXUS ATLAS[15] and at least 1,675 on-label patients enrolled into the TAXUS Libertē study.

Medically treated diabetic subset

Data on medically treated diabetic patients will be analyzed per prior agreement with the FDA. The on-label medically treated diabetic patient subset will be analyzed for a prespecified 12-month TVF rate (defined as any revascularization of the target vessel, MI related to the target vessel, or cardiac death related to the target vessel; see Online Appendix D).

Based on the observed TVF rate of 7.1% from the TAXUS ARRIVE registries,[3] with an adjustment of 1.9% for mandatory cardiac enzyme collection in diabetic patients in the TAXUS Libertē Post-Approval Study, the expected 12-month TVF rate for on-label medically treated diabetic patients treated with TAXUS Liberté is 9.0%.[18] The performance goal is 12.6% using a margin of 3.6%. Given a 1-sided 5% significance level, a minimum of 470 on-label medically treated diabetic patients will be required to provide at least 80% power to meet the TVF performance goal of 12.6%. Considering that there will be 1,512 on-label patients available for 12-month analysis, we estimate that there will be approximately 484 TAXUS Liberté on-label medically treated diabetic patients available for analysis based upon the historical rate of 32% medically treated diabetic patients enrolled in TAXUS ARRIVE.

Study organization and ethical considerations

Data from all patients with MACCE, ST, or major bleeding events (severe or moderate by GUSTO classification[14]) as well as an additional random 20% sampling of patients per site, will be monitored by Boston Scientific. The institutional review board at each participating center will approve the study protocol, and all subjects will provide written informed consent before enrollment. An independent clinical events committee will adjudicate all reported events of all-cause death, major cardiac

Table II. TAXUS Libertē Post-Approval Study secondarly end points

MACCE*
Cardiac death, MI, or stroke
Stroke
MACE†
Cardiac death or MI‡
Cardiac death
MI
TVR
TVF§
All deaths or MIs
All-cause death
Noncardiac death
ST‖
ARC definite or probable
Historic TAXUS trials definition
Bleeding complications (GUSTO criteria)
Severe
Moderate
Major (severe or moderate)¶

Secondary end points measured for all patients at ≤24 hours; 30 days; 6, 12, 15, 24, 30, and 33 months; and annually through 5-year postindex stent implantation. Overall and TAXUS Liberté stent–related rates will be determined for the end points, where applicable. *MACE*, major adverse cardiac events.
* Cardiac death, MI, TVR, or stroke.
† Cardiac death, MI, or TVR.
‡ Primary end point at 12 months.
§ Target vessel failure (target vessel–related death, MI, or revascularization) analysis will also include 12-month rate for TAXUS Liberté on-label diabetic patients.
‖ Analyses will only include overall, TAXUS Liberté on-label, and TAXUS Liberté off-label patients.
¶ Per protocol, major bleeding is defined as a severe or moderate bleeding complication based upon GUSTO classification.[14]

and cerebrovascular events (cardiac death, MI, TVR, stroke), bleeding events, and ST. An independent data monitoring committee is responsible for oversight of all reported adverse events and aggregates safety data to monitor for incidence of serious adverse events and other trends that may warrant modification or termination of the study by the executive committee. Study organization and oversight committee membership are listed in Online Appendix F.

Limitations of the study design

Several limitations will be considered when interpreting the study results. (1) The TAXUS Libertē Post-Approval Study uses historical controls as comparators for the primary end point. Despite the use of propensity score methodology, historical data may be prone to bias because of differences in patient complexity or treatment patterns between TAXUS Liberté and TAXUS Express. (2) Patients in the historical comparator groups were prescribed thienopyridines commercially available at the time of enrollment into the TAXUS ATLAS and ARRIVE studies, whereas the TAXUS Libertē Post-Approval Study uses the more recently approved prasugrel. The use of this newer thienopyridine may affect clinical outcomes and, thus, may potentially confound the interpretation of stent efficacy outcomes. It will be important to examine ST and bleeding rates in this study in the context of previously published results of prasugrel use with DESs.[8] (3) Because of the exclusion of a few high-risk patient conditions (see Appendix A), results may not be generalizable to all potential stent patients.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents. The study is registered at http://www.clinicaltrials.gov, identifier NCT00997503.

Study summary and status

The TAXUS Libertē Post-Approval Study will provide long-term data on the use of the TAXUS Liberté paclitaxel-eluting stent with concomitant prasugrel antiplatelet therapy in unselected patients from routine clinical practice, providing safety and efficacy data in more complicated clinical settings and coronary lesions than what were represented in pivotal randomized TAXUS Liberté trials. Approximately 4,200 patients will be prescribed prasugrel and aspirin for 12 months after stent implantation, making this study the first study to assess prasugrel use in unselected patients receiving the TAXUS Liberté stent. The study will assess a 12-month primary end point of cardiac death or MI compared with a historical group of patients treated with the TAXUS Express stent (in on-label stent indications). In addition, as a major secondary end point, the study is powered to assess annual incremental ST rates through 5 years in patients treated with the TAXUS Liberté stent compared with a performance goal based on the TAXUS Express stent. Other end points include all-cause death, stroke, revascularization, and bleeding in both on- and off-label stented patients. In addition, for the first time, a maintenance dose of 5-mg prasugrel will be assessed in patients ≥75 years old or <60 kg in weight, previously identified as being at greater risk of bleeding after prasugrel use at 10 mg. After 12 months of open-label prasugrel treatment, eligible patients will be randomized to either placebo plus aspirin or an additional 18 months of prasugrel plus aspirin, with data being contributed to the larger randomized DAPT study designed to investigate the optimal duration of dual antiplatelet therapy after PCI with DES placement for the treatment of coronary artery lesions.[9] The TAXUS Libertē Post-Approval Study will therefore provide long-term use information on the utility of TAXUS Liberté paclitaxel-eluting stent implantation with prasugrel antiplatelet therapy in a broad spectrum of stent recipients in addition to providing data regarding the optimal prasugrel dose and duration in high-risk patient subsets.

The first patient in the TAXUS Libertē Post-Approval Study was enrolled in December 2009; as of September 2011, >4,000 patients have been enrolled in the United States. Enrollment completion is projected for December 2011, and primary end point data should be first available in mid 2013.

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Disclosures

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Appendix A

TAXUS Libertē Post-Approval Study inclusion and exclusion criteria

Inclusion criteria

>18 y old
Consecutive patients who have signed an informed consent form, who do not otherwise meet applicable exclusion criteria, and who are eligible to receive a TAXUS Liberté stent and the study-required dual antiplatelet therapy will be evaluated for enrollment in this study.

Exclusion criteria

Known hypersensitivity to paclitaxel or structurally related compounds
Known hypersensitivity to the polymer or any of its individual components
Lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device
Cannot receive the protocol required dual antiplatelet therapy
On warfarin or similar anticoagulant therapy
Known pregnancy
Current medical condition with a life expectancy of <3 y
Currently enrolled in another device or drug study whose protocol specifically excludes concurrent enrollment or that involves blinded placement of a DES other than the TAXUS Liberté stent
Unable to cooperate with prolonged dual antiplatelet therapy
Unable to give informed consent
Inappropriate for randomization because of other conditions requiring chronic thienopyridine use
Treated with both a DES and BMS during the index procedure
Experienced a prior TIA or a prior stroke
Requiring chronic daily use (>2 consecutive weeks) of NSAIDs with the exception of aspirin; occasional use of NSAIDs on an as-needed schedule is not exclusionary
Active pathologic bleeding (such as peptic ulcer or intracranial hemorrhage)

Additional exclusion criteria (applicable only after patient enrollment has reached 3600)

MI within 72 h before the index procedure
History of (includes current) left main coronary artery disease
Stenting of >1 vessel with a TAXUS Liberté stent required during the index procedure
Stenting of >2 vessels required during the index procedure
Staged procedure within 6 wk after the index procedure, with >1 vessel was stented during the index procedure
Cardiogenic shock.
Acute or chronic renal dysfunction (serum creatinine >3.0 mg/dL or patient receiving dialysis)
Target lesion that meets any of the following criteria:
  Located within a saphenous vein graft or an arterial graft
  Chronic total occlusion
  Restenosis from a previously implanted DES or BMS
  Previous use of intravascular brachytherapy in target vessel
  Lesion involves a bifurcation
  Lesion is ostial in location
  Severe tortuosity in the target lesion or target vessel proximal to the target lesion
  Moderate or severe calcification by visual estimate in the target lesion or target vessel proximal to the target lesion
  RVD <2.5 mm or RVD >3.75 mm
  Lesion length >28 mm

TIA, Transient ischemic attack; *NSAIDS*, nonsteroidal anti-inflammatory drugs.

Appendix B

TAXUS Libertē Post-Approval Study randomization inclusion and exclusion criteria at 12 months

Inclusion criteria*

Free from all deaths at 12 m
Free from MI at 12 m
Free from stroke at 12 m
Free from repeat coronary revascularization at 12 m
Free from ST at 12 m
Free from GUSTO severe or moderate major bleeding[16] at 12 m
Prasugrel compliance through 12 m (between 80% and 120% of prasugrel is taken in both the 0-6 m and 6-12 m periods without an interruption of therapy >14 consecutive d)

Exclusion criteria

Known pregnancy
Switched from prasugrel to other thienopyridine after discharge from index hospitalization
Switched maintenance dose of prasugrel within 6 m before randomization
PCI or cardiac surgery between 6 wk postindex procedure and randomization
Planned surgery necessitating discontinuation of antiplatelet therapy within the 21 m after randomization
On warfarin or similar anticoagulant therapy
Current medical condition with a life expectancy of <3 y

Adapted from Mauri et al.[9]
* Patients who experience repeat PCI, MI, or ST within 6 weeks after the index procedure will be eligible for randomization at 12 months.

Appendix C

TAXUS Libertē Post-Approval Study subset analyses

Potential subsets (at least 200 enrolled patients)

On-label patients
Off-label patients
Treated with 10-mg prasugrel maintenance dose
Treated with 5-mg prasugrel maintenance dose
Lesions in the setting of STEMI
Patients with acute coronary syndrome/unstable angina
Elective patients treated with planned PCI
Long lesions
Multiple overlapping stents
Bifurcation lesions
Patients with diabetes
Patients with renal insufficiency
Patients with 2 or 3 vessels treated
Left main lesions
Patients with TOs
Stenting of aortocoronary saphenous vein grafts
Stenting postbrachytherapy
In-stent (BMS) restenotic lesions
In-stent (DES) restenotic lesions
Patients with left ventricular dysfunction with EF <25%
Patients receiving a single 2.25-mm (diameter) stent

(*continued on next page*)

(*continued*)

Potential subsets (at least 200 enrolled patients)
Patients receiving multiple stents, including 2.25-mm (diameter) stent(s)
Patients receiving a single 38-mm (length) stent
Patients receiving multiple stents, including 38-mm (length) stent(s)
On-label diabetic patients with a single 2.25-mm (diameter) stent
On-label diabetic patients with multiple stents, including 2.25-mm (diameter) stent(s)
On-label diabetic patients with a single 38-mm (length) stent
On-label diabetic patients with multiple stents, including 38-mm (length) stent(s)
Randomized patients (at 12 m)
Nonrandomized patients (at 12 m)
Complex patients
Noncomplex patients
Male gender
Female gender

STEMI, ST-elevation MI; *TO*, total occlusion; *EF*, ejection fraction.

Appendix D

TAXUS Libertē Post-Approval Study definitions

ACS	*ACS* is defined as ischemic symptoms occurring at rest and lasting ≥10 min and occurring within 72 h before index procedure and either ST-segment deviation of ≥1 mm or elevated levels of a cardiac biomarker of necrosis (CK-MB or troponin T or I greater than the ULN. If CK-MB or troponin is not available, total CK >2 times ULN). Subjects with STEMI can be enrolled at any time and will be classified as ACS and therefore complex within 14 d after onset of symptoms.
Bifurcation lesion	Lesions where a branch vessel of medium or large size originates.
Bleeding classification	GUSTO Major bleeding end point will be defined by the GUSTO classification of "severe" or "moderate" as defined below: Severe or life-threatening: either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention Moderate: bleeding that requires blood transfusion but does not result in hemodynamic compromise Mild: bleeding that does not meet criteria for either severe or moderate bleeding Bleeding events that are medically important but do not meet the severe/moderate levels will be collected (eg, require laboratory testing, evaluation by a physician, ED visit, or cessation of either study medication or other antithrombotic therapies).
Braunwald classification of unstable angina	Severity Class I: new onset, severe, or accelerated angina. Patients with angina of <2 m duration, severe or occurring ≥3 times per day, or angina that is distinctly more frequent and precipitated by distinctly less exertion; no pain at rest in the last 2 m. Class II: angina at rest, subacute. Patients with ≥1 episodes of angina at rest during the preceding month but not within the preceding 48 h. Class III: angina at rest, acute. Patients with ≥1 episodes of angina at rest within the preceding 48 h. Clinical circumstances Class A: secondary unstable angina. A clearly identified condition extrinsic to the coronary vascular bed that has intensified myocardial ischemia (eg, anemia, fever, infection, hypotension, tachyarrhythmia, thyrotoxicosis, and hypoxemia secondary to respiratory failure). Class B: primary unstable angina Class C: a postinfarction unstable angina (within 2 wk of documented MI)
Calcification	Readily apparent densities seen within the artery wall and site of lesion either as an x-ray absorbing mass or as an echogenic and shadow generating mass in IVUS imaging; these can be classified as little/none, moderate, or severe.
CCSC of angina	Class 1: ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation. Class 2: slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, in wind, under emotional stress, or any only during the first hours after awakening. Walking >2 blocks on the level and climbing >1 flight of ordinary stairs at a normal pace and in normal conditions. Class 3: marked limitations of ordinary physical activity. Walking 1-2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace. Class 4: inability to carry on any physical activity without discomfort; angina syndrome may be present at rest.
Cardiogenic shock	A clinical state of hypoperfusion characterized by systolic pressure <80 mm Hg and/or central filling pressure >20 mm Hg or cardiac index <1.8 L/min per m^2 where there is evidence of insufficient end-organ profusion. Shock is also considered present if intravenous inotropes and/or intraaortic balloon pump are needed to maintain a systolic blood pressure >80 mm Hg and a cardiac index >1.8 L/min per m^2.
CVA or stroke	*CVA* is defined as the occurrence of cerebral infarction (ischemic stroke) or intracerebral and subarachnoid hemorrhages (hemorrhagic stroke). *Stroke* is defined as sudden onset of vertigo, numbness, dysphasia, weakness, visual field defects, dysarthria, or other focal neurologic deficits due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm that either 1. persists >24 h or results in death in <24 h or 2. persists <24 h duration if the following treatments were used: a. pharmacologic, that is, thrombolytic drug administration, or b. nonpharmacologic, that is, neurointerventional procedure (eg, intracranial angioplasty) 3. persists <24 h but has neuroradiological (MRI or CT) diagnostic changes suggestive of acute tissue injury
Chronic total occlusion	Lesion that has been totally occluded for ≥3 m and with a documented TIMI flow of 0
Clinical angiographic success	Mean lesion diameter stenosis <50% (<30% for stents) in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of prolonged chest pain or ECG changes consistent with MI.
Clinical procedural success	Mean lesion diameter stenosis <30% in 2 near-orthogonal projections with TIMI 3 flow, as visually assessed by the physician, without the occurrence of in-hospital MI, TVR, or cardiac death

Death	*Cardiac death* is defined as death due to any of the following: 1. AMI 2. cardiac perforation/pericardial tamponade 3. arrhythmia or conduction abnormality 4. CVA through hospital discharge or CVA suspected of being related to the procedure 5. death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery 6. any death in which a cardiac cause cannot be excluded *Noncardiac death* is defined as a death not due to cardiac causes (as defined above).
Edge stenosis	This is the presence of restenosis in the 5-mm segments proximal or distal to the stent.
Focal stenosis	This is the presence of restenosis with a length <10 mm
Gap stenosis	This is the presence of restenosis between 2 stents (which are <10 mm apart).
In-stent stenosis	The presence of restenosis within the stented segments, either focal (defined by restenosis with a length ≤10 mm) or diffuse (defined by restenosis >10 mm or total occlusion)
Killip classification of AMI	Class I: includes individuals with no clinical signs of heart failure Class II: includes individuals with rales in the lungs, an S_3 gallop, and elevated jugular venous pressure Class III: describes individuals with frank pulmonary edema Class IV: describes individuals in cardiogenic shock
MACCE	Composite of cardiac death, MI, TVR, and stroke
MACE	Composite of cardiac death, MI, and TVR
Major bleeding	A severe or moderate bleeding complication (based upon GUSTO classification)
Metabolic syndrome	Metabolic syndrome is diagnosed when ≥3 of the following measures are present: Central obesity: waist circumference: female >88 cm (35 in), male >102 cm (45 in) Fasting glucose: ≥100 mg/dL Triglycerides: ≥150 mg/dL HDL-Chol: female <50 mg/dL; male ≤40 mg/dL Blood pressure ≥135/85
MI	Historic TAXUS definition—used in primary end point analysis One of the following criteria must be met: CK >2× ULN with positive CK-MB CK >5× ULN with positive CK-MB for post-CABG cases ECG evidence of new pathologic Q waves (lasting ≥0.4 s) in 2 contiguous leads with positive CK-MB

ARC definition

Classification	Biomarker criteria	Additional criteria
Periprocedural PCI (within 48 h after PCI)	Troponin >3 times URL or CK-MB >3 times URL	Baseline value <URL
Periprocedural CABG (within 72 h after CABG)	Troponin >5 times URL or CK-MB >5 times URL	Baseline value <URL and any of the following: new pathologic Q waves or LBBB, new native or graft vessel occlusion, imaging evidence of loss of viable myocardium
Spontaneous (>48 h after PCI, >72 h after CABG)	Troponin >URL or CK-MB >URL	Baseline value <URL and any of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new LBBB), development of pathologic Q waves, or imaging evidence of a new loss of viable myocardium or a new regional wall motion abnormality.
Silent	No biomarker data available	New pathologic Q waves or LBBB
Sudden death	Death before biomarkers obtained or before expected to be elevated	Symptoms suggestive of ischemia and any of the following: new ST elevation or LBBB, documented thrombus by angiography, or autopsy.
Reinfarction, spontaneous and periprocedural (base definition) (infarction extension)	Stable or decreasing values on 2 samples >6 h apart and 20% increase 3-6 h after a second sample	If biomarkers are not stable (increasing or peak not reached) then insufficient data to diagnose recurrent MI.

Renal disease	Serum creatinine >3.0 mg/dL or dialysis
Restenosis	A >50% reduction in diameter of a previously treated lesion when compared with the reference luminal diameter.
ST	Historic TAXUS definition The occurrence of any of the following: 1. Clinical presentation of ACS with angiographic evidence of ST • Angiographic documentation of acute complete occlusion (TIMI flow 0 or 1) of a previously successfully treated artery (TIMI flow 2-3 immediately after stent placement and diameter stenosis ≤30%) and/or • Angiographic documentation of a flow limiting thrombus within or adjacent to a previously successfully treated lesion 2. AMI in the distribution of the treated vessel. 3. Death within the first 30 d postindex procedure (without other obvious cause) is considered a surrogate for ST when angiography is not available. Classification 1. "Confirmed ST" for the description of above events with angiographic evidence.

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(*continued*)

	2. "Presumed ST" for the description of above events in the absence of an angiography (ie, such as in the case of death without autopsy). Timing 1. "Acute" ≤24 h after the study procedure 2. "Subacute" >24 h to ≤30 d after the study procedure 3. "Late" >30 to ≤ 180 d after the study procedure 4. "Very late" >180 d after the study procedure ARC definition ST may be defined as: 1. Confirmed/definite (either angiographic or pathologic confirmed) • Angiographic-confirmed ST is considered to have occurred if a. TIMI flow is 1. TIMI flow grade 0 with occlusion originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of thrombus. 2. TIMI flow grade 1, 2, or 3 originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus. and at least one of the following criteria, up to 48 h, has been fulfilled: b. new onset of ischemic symptoms at rest (typical chest pain with duration >20 min) c. new ischemic ECG changes suggestive of acute ischemia d. typical rise and fall in cardiac biomarkers (>2× ULN of CK) The incidental angiographic documentation of stent occlusion in the absence of clinical syndromes is not considered a confirmed ST (silent thrombosis) 2. Probable • clinical definition of probable ST is considered to have occurred in the following cases: a. any unexplained death within the first 30 d b. any MI in the absence of any obvious cause related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST 3. Possible • clinical definition of possible ST is considered to have occurred with any unexplained death beyond 30 d Timing ST will be reported at different separate time points and as a cumulative value. *Time 0* is defined as the time point after the guiding catheter has been removed and the patient has left the catheterization laboratory. 1. Acute ST (*): 0-24 h poststent implantation 2. Subacute ST (*): >24 h to 30 d poststent implantation 3. Late ST: >30 d to 1-y poststent implantation 4. Very late ST: >1-y poststent implantation (*) acute/subacute can also be replaced by early ST (0-30 d)
ST elevation	ST-segment elevation >0.1 mV in at least 2 contiguous precordial leads or 2 adjacent limb leads
Target lesion	Any lesion treated or attempted to be treated with a TAXUS Liberté stent during the index or staged procedure(s)
TVF	*TVF* is defined as any revascularization of the target vessel, MI (Q and non–Q wave) related to the target vessel, or death related to the target vessel For the purposes of this protocol, if it cannot be determined with certainty whether MI or death was related to the target vessel, it will be considered TVF.
TVR	Any attempted or successfully completed percutaneous or surgical revascularization of a target vessel.
Technical success	Successful delivery and deployment of the study stent to the target vessel, without balloon rupture or stent embolization
Total occlusion	Lesion with no flow (TIMI 0)
TIA	A focal ischemic neurologic deficit of abrupt onset and of presumed vascular etiology that resolves completely within 24 h of onset.

ACS, Acute coronary syndrome; *CK*, creatine kinase; *IVUS*, intravascular ultrasound; *ED*, emergency department; *CCSC*, Canadian Cardiovascular Society Classification; *CVA*, cerebrovascular accident; *MRI*, magnetic resonance imaging; *CT*, computed tomography; *TIMI*, thrombolysis in myocardial infarction; *ECG*, electrocardiogram; *MACE*, major adverse cardiac event; *HDL-Chol*, high-density lipoprotein cholesterol; *ULN*, upper limit of normal; *URL*, upper reference level; *CABG*, coronary artery bypass graft; *LBBB*, left bundle branch block.

Appendix E

Propensity score methodology

Potential baseline covariates for propensity score analysis

Gender, age, prior PCI, prior CABG, prior MI, history of multivessel disease, congestive heart failure, cigarette use (current smoker), hyperlipidemia, hypertension, renal disease, coronary artery location (LAD, RCA, CX),preprocedure RVD, lesion length lesion calcification (moderate/severe), thrombus present at baseline, vessel tortuosity (moderate/severe), chronic total occlusion, lesion type B2/C, number of lesions treated, number of vessels treated, stent implantation pressure, and anti-platelet usage at procedure.

Propensity score subclassification

The propensity score will be estimated by using logistic regression with inclusion of all covariates in the model as the predictor variables and the treatment as the outcome.

The entire study analysis set will be divided into propensity score quintiles or 5 equal-size subclasses. The primary end points will be calculated by study group within each subclass. The adjusted measure for each study group is a simple mean of the 5 propensity score subclass estimates. Similarly, the stratified between-group difference estimate is the mean of the subclass difference estimates, and the adjusted SE is obtained from the square root of the mean of the 5 subclass variances.

LAD, Left anterior descending; *RCA*, right coronary artery; *CX*, circumflex artery.

Appendix F. TAXUS Libertē Post-Approval Study organization

Study sponsor: Boston Scientific Corporation

Cosponsors: Eli Lilly & Company (Indianapolis, IN) and Daiichi Sankyo, Inc (Edison, NJ)

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