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FDA PANEL PROCESS

Overview of the 2016 U.S. Food and Drug Administration Circulatory System Devices Advisory Panel Meeting on the Absorb Bioresorbable Vascular Scaffold System

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ABSTRACT

OBJECTIVES This study aims to describe the discussions and recommendations made during the U.S. Food and Drug Administration (FDA) Circulatory System Device Panel pre-market approval application for the Absorb Bioresorbable Vascular Scaffold (BVS) System.

BACKGROUND The Absorb BVS System is a first-of-its-kind fully bioresorbable percutaneous coronary intervention technology. The absorb BVS was studied in the ABSORB III (A Clinical Evaluation of Absorb BVS, the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects with de Novo Native Coronary Artery Lesions) trial, the pivotal U.S. investigational device exemption trial.

METHODS Observational report of the FDA Circulatory System Device Panel pre-market approval application meeting held on March 15, 2016.

RESULTS The U.S. FDA Circulatory System Device Panel members reviewed the ABSROB III trial outcomes and additional post hoc analyses presented by the sponsor and the FDA. The ABSORB III trial met the primary endpoint of noninferiority of Absorb BVS compared with the control, XIENCE drug-eluting stent, for target lesion failure at 1 year. Although a higher numerical trend for adverse outcomes was reported for the Absorb BVS, there were no statistical differences between Absorb BVS and XIENCE for any safety or effectiveness components for target lesion failure or for the secondary pre-specified outcomes. Panel members raised concerns with regard to the ABSORB III results and post hoc analyses focusing mainly on the noninferiority design of the trial, the apparent safety issues of the Absorb BVS in small vessels, the mismatch of visually versus intravascular imaging assessed vessel size found in ABSORB III and its implications on the adequate device labeling, the safety of Absorb BVS in specific patient and lesion subsets, and the post-approval commitments of the sponsor.

CONCLUSIONS Following panel discussions and the evidence presented, the panel voted for approval of the device. (J Am Coll Cardiol Intv 2016;9:1757–64) © 2016 by the American College of Cardiology Foundation.

The Absorb Bioresorbable Vascular Scaffold (BVS) System (Abbott Vascular, Santa Clara, California) is a first-of-its-kind fully bioresorbable percutaneous coronary intervention technology (1). The ABSORB III (A Clinical Evaluation of Absorb BVS, the Everolimus Eluting Bioresorbable Vascular Scaffold in the Treatment of Subjects With de Novo Native Coronary Artery

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ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stent(s)

BVS = bioresorbable vascular scaffold

DES = drug-eluting stent(s)

FDA = U.S. Food and Drug Administration

MI = myocardial infarction

PMA = pre-market approval application

QCA = quantitative coronary angiography

RVD = reference vessel diameter

TLF = target lesion failure

Lesions) trial (2) was the United States' pivotal investigational device exemption trial. The Absorb BVS was reviewed by the Division of Cardiovascular Devices, Center for Devices and Radiological Health, U.S. Food and Drug Administration (FDA) under a pre-market approval application (PMA) and submitted to the Circulatory System Devices Advisory Panel (hereinafter referred to as the panel) meeting, which was held on March 15, 2016. This summary aims to describe the discussions and recommendations made during the panel meeting with respect to the reasonable assurance of safety and effectiveness of the Absorb BVS marketing in the United States.

ABSORB SYSTEM CLINICAL RESEARCH PROGRAM

NON-U.S. CLINICAL STUDIES. The first-in-human ABSORB Cohort A study (3) enrolled 30 patients. At the 6-month follow-up, the angiographic in-stent late loss was 0.44 ± 0.35 mm and was mainly due to a mild reduction of the cross sectional area of the stented region (-11.8%) as measured by intravascular ultrasonography. Late lumen loss was lower compared with historical bare-metal stent (BMS) data, but was greater than historical XIENCE results. The increased BVS late loss versus XIENCE was believed to have been due to premature loss of scaffold structural integrity and radial strength. This outcome led to a modification in the BVS design, and thus the cohort A study results were not reviewed further by the panel. Subsequently, the results of ABSORB Cohort B (4) (n = 101) at 6 months showed that the cross-sectional area of the stented region was reduced by only 2.0% with intravascular ultrasonography. The late lumen loss amounted to 0.19 ± 0.18 mm with a limited relative decrease in minimal luminal area of 5.4% on IVUS. Optical coherence tomography at follow-up showed that 96.8% of the struts were covered with endothelium. The ABSORB EXTEND (ABSORB EXTEND Clinical Investigation: A Continuation in the Clinical Evaluation of the ABSORB Bioresorbable Vascular Scaffold (BVS) System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions) study (5) included 800 patients. At 1 year, the composite endpoints of ischemia-driven major adverse cardiac events, composed in these series of trials of cardiac death, myocardial infarction (MI), and ischemia-driven target lesion revascularization and ischemia-driven target vessel failure were 4.3% and 4.9%, respectively, and the cumulative rate of definite and probable scaffold thrombosis was 0.8%. The ABSORB II trial (6) randomized 501 subjects to the Absorb BVS (n = 335) or the XIENCE (n = 166). The 1-year composite device orientated endpoint was not significantly different between the BVS and XIENCE (n = 16 [5%] vs. n = 5 [3%], respectively; p = 0.35) and similarly, nonsignificant outcome rates were observed for the combined secondary outcome of target vessel failure (n = 18 [5%] vs. n = 8 [5%], respectively; p = 0.78), or for its components of cardiac death, all MI and ischemia-driven target lesion revascularization. Similar noninferiority results versus everolimus-eluting stents were reported in the ABSORB Japan (7) the ABSORB China (8) trials.

U.S. CLINICAL STUDIES. The results of the ABSORB III (2) were the primary focus of the FDA's evaluation of the PMA. The primary endpoint was target lesion failure (TLF) at 1 year defined as the composite of cardiac death, target vessel-MI, or ischemia-driven target lesion revascularization. The ABSORB III included 2008 subjects (**Figure 1**) randomized to Absorb BVS (n = 1,322, 1,385 lesions treated) or XIENCE (n = 686, 713 lesions treated). For the intention to treat population, the 1-year TLF rates in the Absorb BVS and XIENCE groups were 7.8% and 6.1%, respectively (**Table 1**), and the difference between the 2 study groups was 1.7% with corresponding 95% confidence interval (CI) of (-0.51% to 3.93%), the upper bound of which was less than the pre-specified noninferiority margin of 4.5%. Therefore, the noninferiority endpoint for the Absorb BVS versus XIENCE was met (p = 0.007). Although all components of the TLF were numerically higher for Absorb BVS, none of them achieved statistical significance.

PANEL DELIBERATIONS

All authors of the present review attended the meeting. The meeting was chaired by Dr. Richard Page and initiated with presentations by the sponsor and the FDA. The sponsor, represented by its chief medical officer, Dr. Charles Simonton, suggested the following labeling: "The Absorb GT1 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 (RVD) of ≥2.5 mm and ≤3.75 mm." In view of the known inaccuracies in the visual estimation of RVD, the sponsor also suggested the following precaution and warning: "Precaution: In