Summary of Safety and Effectiveness Data
Bio*divYsio*™ AS PC (phosphorylcholine) Coated Stent Delivery System
(Bio*divYsio*™ AS)

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PC (phosphorylcholine) Coated Stent Delivery System

1. General Information

Device Generic Name:	Intravascular Coronary Stent
Device Trade Name:	BiodivYsio™ AS PC (phosphorylcholine) Coated Stent Delivery System (BiodivYsio™ AS)
Applicants' Name and Address:	Biocompatibles Cardiovascular Inc. Price Waterhouse Cooper LLP Ten Almaden Boulevard Suite 1600 San Jose, CA 95113
PMA Application Number:	P000011
Date of Panel Recommendation:	Not Applicable
Date of Notice of Approval to the Applicant:	SEP 2 9 2000

2. Indications for Use

The 15 mm BiodivYsio™ AS is intended for use in subjects with symptomatic ischemic heart disease due to *de novo* native coronary artery lesions (length ≤25 mm) with a reference vessel diameter ranging from ≥3.0 mm to ≤4.0 mm and intended to improve coronary luminal diameter. Long-term outcome (beyond 6 months) for this permanent implant is unknown at present.

3. Contraindications

Bio*divYsio*™ AS is contraindicated for use in:

- Patients with intolerance or contraindication to antiplatelet or anticoagulant therapy.
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon.

4. Warnings and Precautions

See WARNINGS and PRECAUTIONS in the final draft labeling (Instructions for Use).

5. Device Description

The Bio*divYsio*™ AS is a flexible, balloon-expandable PC-coated stent composed of laser-cut 316L implant grade stainless steel metal tubing mounted on a semi-compliant balloon catheter between two radiopaque marker bands. The stent is coated with a sub-micron thickness of a cross-linked phosphorylcholine ("PC") polymer. The Bio*divYsio*™ AS stent delivery system is used to carry the stent through the coronary vasculature to the target lesion where the stent is deployed as the balloon is inflated. The Bio*divYsio*™ AS is available in nominal diameters of 3.0, 3.5 and 4.0 mm. The Bio*divYsio*™ AS is compatible with PTCA guide wires $\leq$ 0.014"/0.356 mm and PTCA guide catheters $\geq$ 6F (I.D. 0.062"/1.57 mm).

Table 1: Product Labeling Specifications for the Bio*divYsio*™ AS

Delivery System Type	Stent Diameter (mm)	Stent Length (mm)	Crimped Stent Profile (mm)	Guiding Catheter Diameter (F)	Recommended Stent Deployment Pressure (atm)	Rated Burst Pressure (atm)	Nominal Expanded Stent Length (mm)
RX	3.0 3.5 4.0	15	1.17 1.22 1.27	6	8	14	14.5

6. Alternative Practices or Procedures

In addition to coronary artery bypass graft (CABG) surgery, there are several types of stents from various manufacturers on the market, many types of percutaneous transluminal coronary angioplasty (PTCA), or balloon angioplasty devices, several types of atherectomy devices and excimer lasers.

7. Marketing History

The Bio*divYsio*™ AS is approved and marketed internationally in specific countries as follows:

Argentina	Denmark	Israel	Philippines
Australia	Egypt	Italy	South Africa
Austria	Finland	Liechtenstein	Spain
Belgium	France	Luxembourg	Sweden
Brazil	Germany	Mexico	Switzerland
Canada	Greece	Netherlands	Turkey
Chile	Hong Kong	New Zealand	United Kingdom
Colombia	Iceland	Norway	Uruguay
Croatia	India	Pakistan	
Czech Republic	Ireland	Portugal	

The Bio*divYsio*™ AS device has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

8. Adverse Effects of the Device on Health

A total of 686 patients were enrolled in Biocompatibles Bio*divYsio*™ Stent in Randomized Control Trial (DISTINCT) multicenter trial to evaluate the safety and effectiveness of the Bio*divYsio*™ AS for the treatment of symptomatic coronary artery disease. Of these, 377 received the Bio*divYsio*™ AS and 309 received the ACS Multi-Link Duet Stent. The randomized patients form the basis for the observed events reported.

Table 2: Summary of Clinical Study Patient Enrollments (N=686)

	Bio*divYsio*™ AS Stent	Control Stent	Patients Total
Randomized Clinical Study	313	309	622
Roll in Phase	64	0	64
Patients Total	377	309	686

8.1 Observed Adverse Events

Three patients who were implanted with the Bio*divYsio* AS Stent died during the trial. The deaths occurred between 157 and 197 days post stenting and were due to a cerebral vascular accident, pneumonia and ventricular fibrillation (cardiac arrest). In addition,

three patients experienced out-of-hospital Q wave myocardial infarctions (MI's) and ten patients required coronary artery bypass graft (CABG) surgery.

The incidence of vascular (local) complications in the clinical study was 0.3% (1/312) and the rate for bleeding requiring transfusion was 0.3% (1/312).

Initial delivery failure occurred in 2.9%(9/312), one was a failure to deliver a second stent and eight were failures to deliver the first stent only. In the study there were four occasions (1.3%, 4/312) when the assigned stent was not delivered, one event of each of the following, wrong stent given to investigator, guidewire caused abrupt closure, predilation balloon did not cross lesion and stent size was not available. There were eleven (3.5%) mixed stent implantations, 10 were due to dissection or intimal flap and one due to lesion length.

Of the 64 patients enrolled in the roll-in phase of the trial, one patient died at 213 days post stenting due to colon cancer. In addition, one patient underwent CABG surgery and three patients underwent repeat PTCA.

Table 3: Major Adverse Events (Event Based) – In-Hospital vs. Out-of-Hospital Complications

Complication	Bio*divYsio*™ AS Stent n = 312*	ACS Multi-Link Duet n = 309
Death Total		
Early (In-Hospital)	0.0% (0.0, 1.2) 0/312	0.0% (0.0, 1.2) 0/309
30-Days	0.0% (0.0, 1.2) 0/312	0.0% (0.0, 1.2) 0/309
Out-of-Hospital	1.0% (0.2, 2.8) 3/312	1.0% (0.2, 2.81) 3/309
Q-Wave MI Total		
Early (In-Hospital)	0.0% (0.0, 1.2) 0/312	0.3% (0.0, 1.8) 1/309
Out-of-Hospital	1.0% (0.2, 2.8) 3/312	0.0% (0.0, 1.2) 0/309
Non Q-Wave MI Total		
Early (In-Hospital)	0.6% (0.1, 2.3) 2/312	0.6% (0.1, 2.3) 2/309
Out-of-Hospital	0.6% (0.1, 2.3) 2/312	1.0% (0.2, 2.8) 3/309
CABG Total		
Early (In-Hospital)	0.3% (0.0, 1.8) 1/312	0.0% (0.0, 1.2) 0/309
Out-of-Hospital	2.9% (1.3, 5.4) 9/312	1.3% (0.3, 3.3) 4/309
SubAcute Occlusion Total		
Early (In-Hospital)	0.0% (0.0, 1.2) 0/312	0.6% (0.1, 2.3) 2/309
Out-of –Hospital	0.0% (0.0, 1.2) 0/312	0.0% (0.0, 1.2) 0/309
Bleeding Complications	0.3% (0.0, 1.8) 1/312	0.6% (0.1, 2.3) 2/309
Vascular Complications	0.3% (0.0, 1.8) 1/312	1.3% (0.3, 3.3) 4/309
Stent Delivery Failure	2.9% (1.3, 5.4) 9/312	1.3% (0.3, 3.3) 4/309

Note: One patient was removed from the Bio*divYsio*™ AS analysis because two lesions were treated. Data on 312 patients in randomized phase reported.

8.2 Potential Adverse Events

The following complications relating to PTCA and stenting have been reported and may occur:

- Dissection of coronary artery
- Injury, rupture or other damage to the coronary artery
- Sudden total occlusion of the coronary artery
- Thrombosis of the coronary artery
- Unstable angina
- Arterial spasm
- Myocardial infarct
- Ventricular fibrillation
- Disturbance of cardiac conductibility
- Pseudo aneurysm
- Embolism
- Restenosis of the dilated artery
- Stent migration
- Death
- Drug reactions to anti-platelet agents
- Stent embolism
- Ischemia

9. Summary of Preclinical Studies

9.1 Biocompatibility Testing

The Bio*divYsio*™ AS and the delivery system were tested in accordance with the International Standard ISO 10993-1, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." The Bio*divYsio*™ AS and the delivery system met the applicable tests. The following tests were conducted: sensitization, intracutaneous reactivity, cytotoxicity, acute systemic toxicity, subchronic toxicity, hemocompatibility, pyrogenicity, muscle implantation, and genotoxicity/mutagenicity. The results of all biocompatibility tests were acceptable.

9.2 Sterilization Testing

The process was validated as per EN 550 and ISO 11135:1994(E) and validation confirmed that the sterilization method attained a SAL (Sterility Assurance Level) of 10^{-6}.

9.2.1 EtO Residuals

EtO residuals for the Bio*divYsio*™ AS was determined using a method that complies with ISO 10993-7:1995(E). The residuals levels measured met the requirements of ISO 10993-7:1995(E).

9.3 In-Vivo Animal Testing

Short-term (1-5 days) and long-term (1, 3 and 6 months) *in vivo* animal studies evaluated the functional characteristics and performance of the Bio*divYsio*™ AS (coated and uncoated). Included in these studies were evaluations of early and late patency rates, the biological response of the vessel to the stent and the ability to deliver hand crimped stents using a variety of balloon catheters. The studies showed that the stent could be delivered successfully to sites and can be deployed successfully. Histological and pathological studies did not indicate any abnormalities.

9.4 In-Vitro Bench Testing

9.4.1 Stent Material Specification and Conformance Testing

9.4.1.1 Chemical Analysis

Bio*divYsio*™ AS is fabricated from medical grade 316L stainless steel tubing, which conforms to ASTM F-138-96, in both the chemical analysis and the inclusion/impurity content.

9.4.1.2 Yield Strength and Elongation

The tensile strength was 80-100 kpsi and the nominal elongation in 2 inches is 48%. The vendor provides a Certificate of Analyses and Tests with each lot of stainless steel tube shipped to Biocompatibles; certificates are on file at Biocompatibles.

9.4.1.3 ASTM Conformance

The stainless steel material and corrosion resistance comply with ASTM F139 Rev 92, Grade 2 and ASTM A-262, Practice A specifications, respectively.

9.4.2 Stent Integrity Testing

9.4.2.1 Corrosion

An *in vitro* electrochemical linear polarization (LPR) corrosion test was conducted. Stents were immersed in three different electrolyte solutions and electrically stimulated using a capacitor flash discharge method. Current flow upon discharge was very high and of short duration to minimize heating of the stent. Each stent was cradled in the selected solution. A small voltage was applied to the stent and the current recorded. The current value was used to determine stent resistance to polarization from which a corrosion rate was calculated. The corrosion resistance of stents met the product specification.

9.4.2.2 Dimensions

Stents were inspected at 100x magnification for dimensional conformance. Inspection included a review of strut dimensions for conformance to the specifications. The stents met the product specifications.

9.4.2.3 Stent-Free Area Percentage

The stent free area was calculated by determining the area of a discrete "sub-unit" from AutoCAD and comparing this to the calculated area of an artery, assuming the artery is a regular cylinder equal to length of the stent. The stent-free area was calculated as 83%, 85% and 87% for the 3.0, 3.5 and 4.0 mm stents, respectively. The stents met the product specifications.

9.4.2.4 Length Change

The length change test determined the percent shortening of the Bio*divYsio*™ AS when expanded to the rated burst pressure. The length of five (5) stents of each of the three diameters was measured at baseline and after inflation to the nominal deployment pressure of 8 atm. Stent foreshortening ranged from 0.07% to 2.1% and met the product specification.

9.4.2.5 Uniformity of Expansion

Five (5) stents of each of the three diameters were expanded in 2 atm increments to 16 atm and diameter measurements were made at seven points along the stent. The Bio*divYsio*™ AS expanded uniformly and maintained uniformity upon withdrawal of the balloon catheter. Variation in stent diameter was less than 3% along the length of the stent and met the product specifications.

9.4.2.6 Recoil

Five (5) stents mounted on each of the 3.0 and 4.0 mm diameter balloon catheter were inflated to 4 atm and thereafter in 2 atm increments to 16 atm. At each increment, seven diameter measurements, along the length of each stent, were measured with the balloon inflated. Following a 2-minute minimum interval after balloon deflation, the length and

diameter of each stent is measured again as above. The measurements were made at 100x magnification. Percent recoil was 3% and met the product specifications.

9.4.2.7 Compression – Radial Strength

Five (5) stents of the 3.0 and 4.0 mm diameter stents were expanded and mounted in a pair of "V" blocks and compressed a distance of 1 mm in increments of 0.05 mm. The applied force at each increment was measured. The stress/strain curve was linear up to 1.5 N (approximately 0.8 lbs). The stents met the product specifications.

9.4.2.8 Accelerated Fatigue

The accelerated fatigue test was performed to determine the fatigue resistance of the largest diameter Bio*divYsio*™ AS. Sixteen (16) stents were deployed to 0.25 mm above the maximum recommended deployment diameter of 4.0 mm in latex tubes and subjected to 400 million cycles (equivalent to 10 year heart beats at 72 beats per minute). Latex tube compliance was maintained between 2-3%. The stents were examined by optical microscopic evaluation and SEM. The Bio*divYsio*™ AS successfully completed 400 million cycles accelerated fatigue without collapse or structure failure. The stents met the product specifications.

9.4.2.9 Finite Element Analysis (FEA)

The FEA evaluated the structural integrity of the Bio*divYsio*™ AS when subjected to expected load conditions generated in coronary arteries. The analysis predicted a mean endurance greater than the specified minimum life of 4.0×10^8 cycles and the maximum plastic strain was 35.5% with the stent expanded to 4.25mm. The stents met the product specifications.

9.4.2.10 Magnetic Resonance Imaging (MRI)

All Bio*divYsio*™ AS stents are manufactured from 316L stainless steel. Nickel in 316L stainless steel stabilizes iron in a nonmagnetic state and reduces the potential for stent movement within a magnetic field. The Instructions for Use specifically recommends that a MRI should not be performed until the implanted stent has been completely endothelialized (approximately 8 weeks) in order to minimize stent migration.

9.4.3 Stent and Delivery System Testing

9.4.3.1 Delivery System Profile - Crimped Stent Outer Diameter (OD)

The delivery system profile as the diameter of the crimped stent on a balloon was measured using a LASER micrometer. The profile of the 3.0, 3.5 and 4.0 mm stent-balloon catheters are 1.0, 1.1, and 1.2 mm, respectively. Crimped stent outer diameter met internal requirement.

9.4.3.2 Inflation and Deflation Times Test

Five (5) Bio*divYsio*™ AS stents of each of the 3.0 and 4.0 mm diameters were expanded using the balloon catheter to evaluate balloon deflation and ease of balloon removal. Stents were deployed fully by inflating the balloon catheter to 8 atm. Balloon deflation was observed and balloon withdrawal from the deployed stent was subjectively evaluated. In all cases, the balloon deflation averaged 2.2 and 2.9 seconds for the 3.0 and 4.0 mm balloons, respectively, and catheter removals were found to be satisfactory. This met the product specifications.

9.4.3.3 Balloon and Stent Compliance Test

The data analysis indicated with 95% confidence, 99.9% of the balloons will not rupture at or below their rated burst pressure (RBP) of 14 atm. Twenty–four (24) catheters of each of the three diameters were expanded in 2 atm increments to burst. The balloon RBP of the Bio*divYsio*™ AS met the product specifications. The stent outer diameter was measured at pressure intervals and the correlation between the inflation pressure and the stent outer diameter was determined.

9.4.3.4 Bond Strength

The bond test determined the tensile strengths of the junctions. The test results of the bond strength of the catheter hub junction, catheter shaft and rapid exchange joint were >70 N, 63 N and 14.5 N, respectively. These results exceed the ISO standard (ISO 10555-1) specification and met the product specifications.

9.4.3.5 Delivery System In-Stent Balloon Fatigue Test

Fatigue testing of the balloon catheter was carried out by inflating each test balloon 20 times to the RBP. Twenty-nine (29) catheters of the smallest (3.0 mm) and largest (4.0 mm) were tested by inflating each balloon within a deployed stent. All catheters tested met the requirement. These results indicate that with 95% confidence, 90% of the balloons will not fail repeated inflations to burst pressure.

9.4.4 Package Integrity Testing

The sealing process is validated using seal peel strength testing and visual inspection. Each seal is inspected for voids, channels, holes, or other defects. The pouches are placed in individual labeled cartons; multiple inner cartons are placed in a shipping carton for sterilizing and distribution.

The packaging has been subjected to accelerated aging and shipping trials. All testing was conducted in accordance with GLP regulations and included packaging burst test, package peel strength test, sterility test, and talc challenge test, vibration and drop testing. There are data to support a "use by date" of 75 days from the date of sterilization based on accelerated aging studies.

9.5 Shelf Life (Aging)

Limited functional performance testing and packaging integrity testing was conducted on the Bio*divYsio* AS for product under real time and accelerated aging conditions. Shelf life testing is based on the shelf life of stents implanted in the DISTINCT Trial. The shelf life has been established at 75 days for the Bio*divYsio*™ AS Stent System.

10. Summary of Clinical Studies

A multicenter, prospective randomized trial was conducted at 35 centers in North America (21 in US, 14 in Canada). A total of 686 subjects were enrolled between November 27, 1998 and May 10, 1999 in two phases: 64 subjects in the roll-in phase and 622 in the randomized phase. In the randomized phase, 622 were randomly assigned to either the Bio*divYsio*™ AS group (313) or ACS Multi-Link Duet control group (309). One Bio*divYsio*™ AS patient was removed from the analysis because two lesions were treated.

Data on 312 Bio*divYsio*™ AS patients in the randomized phase are reported. Clinical follow-up at 6 months was obtained in 90.6% of the Bio*divYsio*™ AS group and 97.1% in the ACS Multi-Link Duet group. The first two thirds of the randomized subjects (410) were required to undergo angiographic follow-up at 6 months post procedure (Bio*divYsio*™ AS - 206 patients and ACS Duet – 204 patients). Angiographic follow-up was obtained in 72.3% of the Bio*divYsio*™ AS group and 74.0% in the ACS Multi-Link Duet group. Mean age of the subjects was 60 years, with 71% subjects being males. All other clinical characteristics were similar between the two groups. There was a statistically significant difference in the number of patients with the target lesion located in the left anterior descending (LAD) artery between the Bio*divYsio*™ AS group and the ACS Multi-Link Duet group (46.1% vs. 37.7%).

Computer-assisted Quantitative Coronary Angiography (QCA) was performed at a central core laboratory at baseline, immediately after the procedure in all subjects and again at 6 months on a subset (two thirds), as well as any subjects returning for angiographic evaluation due to signs or symptoms of ischemia. Clinical and angiographic data were analyzed based on an intent-to-treat data set. An independent Clinical Events Committee (CEC) evaluated all MACE, (sub)acute occlusions and bleeding and vascular complications and an independent Data and Safety Monitoring Board (DSMB) evaluated the study progress at predetermined points during the trial.

The anticoagulation regime was acetylsalicylic acid (325 mg / day) prescribed for a minimum of 6 months, ticlopidine, prescribe 250 mg b.i.d. for 2-4 weeks or clopidogrel, prescribed 75 mg q.d. for 28 days.

Follow up intervals were 2, 4 weeks, 6 and 12 months post procedure.

10.1 Population Bias

There were no significant differences between the Bio*divYsio*™ AS and the ACS Multi-Link Duet groups with respect to gender, age, body weight, smoking history, prior MI,

CABG, medical history including diabetes, other concurrent diseases and prior medications.

10.2 Gender Bias

The DISTINCT trial inclusion and exclusion criteria were designed and the study conducted to avoid gender bias in patient enrollment. The higher percentage of male patients enrolled in the study (71% male, 29% female) reflects the gender referral pattern for patients undergoing coronary interventional procedures.

The statistical analysis of the clinical data from the DISTINCT trial did not show an association between gender and the primary and secondary clinical outcomes, including TVF, angiographic binary restenosis, TVR, TLR, clinical device success and procedural success. In addition, MACE rates were comparable in each study in the male and female groups except for repeat PTCA between $\geq$ 30 days and 210 days where a significantly higher rate was observed in female patients compared to males (18.9% vs. 7.2%). These data demonstrate that gender was not an influencing factor on safety or effectiveness.

10.3 Objectives

The purpose of the study was to demonstrate the safety and effectiveness of the Bio*divYsio*™ AS (15 mm Stent) compared to the ACS Multi-Link Duet. The primary objective is to demonstrate that the Bio*divYsio*™ AS is equivalent to the ACS Multi-Link Duet Stent with respect to the 6-month Target Vessel Failure (TVF) rate. It was anticipated that the 6-month TVF rate for the Bio*divYsio*™ AS will be within 7% of the reported 12.3% TVF rate at 6 months for the ACS Multi-Link Stent (based on the ASCENT Trial). TVF includes death, non-fatal myocardial infarction, CABG and repeat PTCA of the original target lesion or target vessel.

10.4 Statistical Analysis

Patients randomized in DISTINCT between the Bio*divYsio*™ AS and ACS Multi-Link Duet underwent comparability analysis in order to confirm that the populations were comparable and to justify pooling of these data prior to the effectiveness and safety analyses.

Once the comparability analysis was complete and the outcome justified data pooling, analyses of effectiveness and safety were performed. The first analysis was by 'intent-to-treat' in which patients were analyzed in the treatment groups to which they were assigned. Analysis based on the treatment patients actually received, i.e. the evaluable patients analysis or per protocol analysis, was not performed.

10.5 Comparability Analysis

Demographic and prognostic characteristics at baseline were compared between the Bio*divYsio*™ AS and the ACS Multi-Link Duet groups to determine if the two groups are comparable. For continuous variables, such as age or lesion length, a two-sample t-test or Wilcoxon rank sum test was used. For categorical variables, such as gender or Angina Class (Canadian Cardiovascular Society Classification or Braunwald Classification), the Pearson's Chi-square or Fisher's exact test was used. Variables found to be statistically significant were included as possible covariates in subsequent safety and effectiveness analyses.

Specific variables assessed for comparability were age, height, weight, gender, history of myocardial infarction, CABG, coronary artery intervention, hypertension, hypercholesterolemia, cardiovascular accident, arrhythmia requiring treatment, diabetes mellitus, congestive heart failure, smoking, and family history of coronary artery disease. Also, baseline angina status and lesion characteristics were compared by examining baseline angina status, reference vessel diameter, target lesion percent diameter stenosis, target lesion minimal lumen diameter and target lesion length.

As part of this comparability analysis, subjects receiving one 15 mm Bio*divYsio*™ AS were compared to those receiving two or more in order to establish poolability of these data. Further, an analysis of baseline characteristics by study site was carried out in order to statistically justify data pooling.

10.6 Analysis of Primary and Secondary Objectives

10.6.1 Primary Objective

The primary objective to establish effectiveness was to show that the Bio*divYsio*™ AS is equivalent to the ACS Multi-Link Duet with respect to 6-month TVF rate. This outcome was based on the hypothesis that the 6-month TVF rate for the Bio*divYsio*™ AS is equivalent to the 6-month TVF rate of the ACS Multi-Link Duet (within 7%) in subjects with *de novo* native coronary lesions, with a lesion length of ≤ 25 mm, and a reference vessel diameter ≥3.0 mm and ≤4.0 mm diameter.

The primary objective of this study was analyzed with a one-sided test of bioequivalence, at the 0.05 level of statistical significance, using the method of Blackwelder. In addition, freedom from TVF is estimated over time using Kaplan-Meier methods. A log-rank test is used to compare the survival curves between the two groups.

For modeling of the TVF rate to adjust for covariates, logistic regression was used. Potential covariates were screened for inclusion into the model with Chi-square or Fisher's exact test for categorical variables and by t-test or Wilcoxon test for continuous variables. Two-factor interactions were screened by modeling paired factors by logistic or Cox regression assessing the main effects and two-factor interaction. Any screened variable or interaction associated with the TVF rate with a P-value less than 0.2 was eligible to enter the model. To be retained in the model, the variable must be significantly associated with the TVF rate with a P-value of 0.05 or less. Initial models will include main effects and two-factor interactions.

10.6.2 Secondary Objectives

The secondary objective of effectiveness is to establish the 6-month binary restenosis rate for the Bio*divYsio*™ AS and ACS Multi-Link Duet. The secondary endpoint of the 6-month angiographic restenosis rate was determined by off-line quantitative coronary angiography (QCA) and is defined as a ≥ 50% reduction in the minimum lumen diameter at 6 months compared to reference vessel minimum lumen diameter.

This secondary objective was analyzed by comparing the rates of 6-month angiographic binary restenosis between treatment and control groups in the angiographic cohort. This was done by confidence interval estimation quantifying the difference in rates at 6 months. This consisted of estimation of the difference of observed rates, estimation of relative risk of restenosis, or estimation of the odds ratio. In addition, freedom from restenosis is estimated over time using Kaplan-Meier methods along with the log-rank test to compare groups.

Adverse event rates for the evaluation of safety were compared between groups at 30 days and 6 months post-procedure. Differences in the rates between groups were estimated with 95% confidence intervals, while ordinal responses like classification of chest pain were addressed using Cochran-Mantel-Haenszel methods or the Wilcoxon test depending on sample size.

Similar to the effectiveness analysis, modeling of adverse event rates to account for covariate adjustment was done by logistic or Cox regression where necessary. The same screening and retention rules given above are used for these analyses.

10.7 Study Design

Subjects with stable angina pectoris (Canadian Cardiovascular Society 1, 2, 3 or 4), or unstable angina pectoris with documented ischemia (Braunwald Class IB-C, IIB-C or IIIB-C), or subjects with documented silent ischemia, who were scheduled to undergo coronary angioplasty of a *de novo* lesion (lesion length ≤25 mm) in a coronary artery suitable for up to two 15 mm Bio*divYsio*™ AS Stents; two 8 mm or 13 mm ACS Multi-Link Duet Stents; or a single 8 mm, 13 mm, 18 mm, 23 mm or 28 mm ACS Multi-Link Duet Stent, were considered candidates for the trial.

During the roll-in phase, subjects were enrolled using the same inclusion/exclusion criteria and protocol requirements for the randomized trial, to ensure adequate experience with implanting the Bio*divYsio*™ AS.

10.8 Description of Patients

In the randomized phase, 622 subjects were randomly assigned to either the Bio*divYsio*™ AS (313) or the ACS Multi-Link Duet (309). One Bio*divYsio*™ AS patient was not part of the analysis because the patient had two lesions treated during the index procedure. There were no significant differences between the Bio*divYsio*™ AS group and ACS Multi-Link Duet group with respect to gender (71.3% vs. 71.2% male), age (60.2 ± 10.3 vs. 59.8 ± 11.2 years), height (67.4 ± 4.0 vs. 67.3 ± 4.0 inches), body weight (187.3 ± 38.7 vs. 187.3 ± 43.1 lbs), current smoker (25.1% vs. 27.0%), prior MI (37.1% vs. 40.8%), prior CABG (3.5% vs. 4.8%), diabetes (21.4% vs. 20.7%), and prior medications (97.4% vs. 98.4%) (see Table 4). The distribution of angina was statistically similar in both groups for stable angina (54.8% vs. 51.8%), unstable angina (43.7% vs. 43.0%), and silent ischemia (6.7% vs. 9.1%). Although other concurrent diseases were found not to be significantly different for specific conditions, a statistically significant difference was detected with the general category "Other Disease" (37.0% vs. 45.6%) for Bio*divYsio*™ AS and ACS Multi-Link Duet, respectively.

Table 4: Baseline Demographics and Clinical Characteristics (Intent to Treat) -All Randomized Patients (N = 622)

Observation	Bio*divYsio*™ AS n=313	ACS Duet n=309	Difference (CI)
Number of Men	71.3% (223/313)	71.2% (220/309)	0.1% (-7.1%, 7.2%)
Mean Age (years) **SD (N)** **Range (min, max)**	60.2 10.3 (313) (35.0, 92.0)	59.8 11.2 (309) (28.0, 87.0)	0.4 (-1.3, 2.1)
Mean Height (inches) **SD (N)** **Range (min, max)**	67.4 4.0 (312) (59.0, 78.0)	67.3 4.0 (308) (51.0, 76.0)	0.1 (-0.5, 0.7)
Mean Weight (lb) **SD (N)** **Range (min, max)**	187.3 38.7 (313) (95.0, 376.2)	187.3 43.1 (308) (102.0, 404.1)	0.0 (-6.5, 6.4)
Current Smoker	25.1% (78/311)	27.0% (83/308)	-1.9% (-8.8%, 5.0%)
Prior MI	37.1% (116/313)	40.8% (126/309)	-3.7% (-11.4%, 3.9%)
Prior CABG	3.5% (11/313)	4.8% (15/309)	-1.3% (-4.5%, 1.8%)
Prior Coronary Artery Intervention	18.2% (57/313)	18.8% (58/309)	-0.6% (-6.7%, 5.5%)
Hypertension	53.4% (166/311)	52.1% (160/307)	1.3% (-6.6%, 9.1%)

Hypercholesterolemia	61.0% (175/287)	62.1% (177/285)	-1.1% (-9.1%, 6.8%)
Prior Cerebral Vascular Accident	4.2% (13/311)	4.9% (15/309)	-0.7% (-3.9%, 2.6%)
Family History Coronary Artery Disease	59.7% (166/278)	59.7% (163/273)	0.0% (-8.2%, 8.2%)
Prior Peripheral Vascular Disease	5.8% (18/308)	7.2% (22/304)	-1.4% (-5.3%, 2.5%)
Arrhythmia Requiring Treatment	7.1% (22/310)	8.4% (26/309)	-1.3% (-5.5%, 2.9%)
Diabetes	21.4% (67/313)	20.7% (64/309)	0.7% (-5.7%, 7.1%)
Insulin Dependent	6.1% (19/313)	5.8% (18/309)	0.3% (-15.2%, 15.7%)
Congestive Heart Failure	5.8% (18/312)	5.2% (16/309)	0.6% (-3.0%, 4.2%)
Other Concurrent Diseases	53.7% (168/313)	57.6% (178/309)	-3.9% (-11.7%, 3.9%)
Renal	5.4% (17/313)	4.9% (15/309)	0.6% (-2.9%, 4.0%)
Liver	0.9% (3/313)	0.3% (1/309)	0.6% (-1.6%, 4.4%)
Cancer	4.1% (13/313)	2.9% (9/309)	1.2% (-1.7%, 4.1%)
Gastro Intestinal	18.2% (57/313)	14.6% (45/309)	3.6% (-2.2%, 9.5%)
Central Nervous System	2.6% (8/313)	2.6% (8/309)	0.0% (-4.9%, 3.6%)
Chronic Obstructive Pulmonary Disease	6.7% (21/313)	8.4% (26/309)	-1.7% (-5.9%, 2.5%)
Other Diseases	37.0% (116/313)	45.6% (141/309)	**-8.6% (-16.3%, -0.9%)**
Prior Medications (within 30 days)	97.4% (305/313)	98.4% (304/309)	-0.9% (-5.7%, 2.2%)
Acetylsalicylic acid	90.1% (282/313)	89.0% (275/309)	1.1% (-3.7%, 5.9%)
Ticlopidine	24.0% (75/313)	25.9% (80/309)	-1.9% (-8.7%, 4.9%)
Dipyridamole	0.6% (2/313)	1.0% (3/309)	-0.3% (-4.2%, 2.3%)
Heparin	24.6% (77/313)	31.4% (97/309)	-6.7% (-13.8%, 0.2%)
Coumadin/Warfarin	1.6% (5/313)	2.6% (8/309)	-1.0% (-5.5%, 2.3%)
Beta Blocker	64.5% (202/313)	68.9% (213/309)	-4.4% (-11.8%, 3.0%)
Ca+ - Antagonist	33.2% (104/313)	32.0% (99/309)	1.2% (-6.2%, 8.6%)
Nitrates	57.8% (181/313)	57.9% (179/309)	-0.1% (-7.9%, 7.7%)
ACE – Inhibitor	21.7% (68/313)	20.7% (64/309)	1.0% (-5.4%, 7.4%)
Diuretics	17.3% (54/313)	16.2% (50/309)	1.1% (-4.8%, 6.9%)
Lipid Lowering	48.2% (151/313)	46.3% (143/309)	1.9% (-5.9%, 9.8%)
Other Cardiac Medications	37.1% (116/313)	37.2% (115/309)	-0.2% (-7.8%, 7.4%)

Angina			
Stable Angina	54.8% (171/312)	51.8% (159/307)	3.0% (-4.8%, 10.9%)
CCSC I	9.4% (16/171)	8.8% (14/159)	0.6% (-5.6%, 6.8%)
CCSC II	44.4% (76/171)	35.2% (56/159)	9.2% (-1.3%, 19.7%)
CCSC III	39.8% (68/171)	45.3% (72/159)	-5.5% (-16.2%, 5.1%)
CCSC IV	6.4% (11/171)	10.7% (17/159)	-4.2% (-10.3%, 1.8%)
Unstable Angina	43.7% (136/311)	43.0% (133/309)	0.7% (-7.1%, 8.5%)
I B	20.6% (28/136)	22.0% (29/132)	-1.4% (-11.2%, 8.4%)
II B	27.9% (38/136)	39.4% (52/132)	**-11.5% (-22.7%, -2.1%)**
III B	27.2% (37/136)	15.2% (20/132)	**12.1% (2.4%, 21.7%)**
I C	8.8% (12/136)	7.6% (10/132)	1.2% (-5.3%, 7.8%)
II C	6.6% (9/136)	9.9% (13/132)	-3.2% (-9.8%, 3.3%)
III C	8.8% (12/136)	6.1% (8/132)	2.7% (-5.2%, 13.4%)
Silent Ischemia	6.7% (21/313)	9.1% (28/309)	-2.4% (-6.6%, 1.9%)
Number of Diseased Vessels			
Single	60.1% (188/313)	58.6% (181/309)	1.5% (-6.2%, 9.2%)
Double	21.7% (68/313)	21.7% (67/309)	0.0% (-6.4%, 6.5%)
Triple	18.2% (57/313)	19.7% (61/309)	-1.5% (-7.7%, 4.6%)

Data are not available for all patients where the denominator is less than 313 for the Bio*divYsio*™ AS group or less than 309 for the ACS Duet group.

There were no significant differences between the Bio*divYsio*™ AS and ACS Multi-Link Duet groups with respect to reference vessel diameter (RVD) (2.9 ± 0.5 vs. 3.0 ± 0.5 mm), minimal lumen diameter (MLD) (0.8 ± 0.4 vs. 0.9 ± 0.4 mm), percent diameter stenosis (% DS) (72.3 ± 11.9 vs. 70.7 ± 13.2 mm) and lesion length (14.5 ± 6.09 vs. 14.1 ± 6.02 mm) (see Table 5). There was a statistically significant difference in the number of patients with the target lesion located in the LAD artery between the Bio*divYsio*™ AS group vs. the ACS Multi-Link Duet group (46.1% vs. 37.7 %).

Table 5: Baseline Angiographic Characteristics (Intent to Treat) -All Randomized Patients (N=621)

Observation	Bio*divYsio* AS n=312	ACS Duet n=309	Difference (CI)
	Mean SD (N)	Mean SD (N)	
Reference Vessel Diameter (mm)	2.9 ± 0.5 (310)	3.0 ± 0.5 (308)	-0.02 (-0.1, 0.1)
Minimal Lumen Diameter (mm)	0.8 ± 0.4 (310)	0.9 ± 0.4 (308)	-0.1 (-0.1, 0.01)
Percent Diameter Stenosis (% DS)	72.3 ± 11.9 (310)	70.7 ± 13.2 (308)	1.6 (-0.4, 3.5)
Lesion Length (mm)	14.5 ± 6.1 (302)	14.1 ± 6.0 (301)	0.4 (-0.6, 1.3)
Target Vessel [% (n/N)]			
LAD	46.1% (143/310)	37.7% (116/308)	8.5% (0.7%, 16.2%)
RCA	32.3% (100/310)	37.7% (116/308)	-4.4% (-12.0%, 3.1%)
Cx	21.6% (67/310)	24.7% (76/308)	-3.1% (-9.7%, 3.6%)

* Baseline angiographic data not available for two Bio*divYsio* AS patients and one ACS Duet patient.
**Data are not available where the denominator is less than 310 for the Bio*divYsio* AS group or less than 308 for the ACS Duet group.
***One Bio*divYsio* AS patient (35-002) is excluded as two lesions were treated during the index procedure.

10.9 Results

There were no significant differences between the Bio*divYsio*™ AS and the ACS Multi-Link Duet groups. A definition on the deliverability of the first intended stent (Technical Device Success) is not statistically significantly different (95.5% vs. 97.7%).

The rate of TVF experienced in patients with the Bio*divYsio*™ AS is equivalent to the TVF rate in patients with the ACS Multi-Link Duet Stent. The angiographic binary restenosis rate is similar in both groups. There are no statistical differences in the principal Effectiveness and Safety measures (see Table 6).

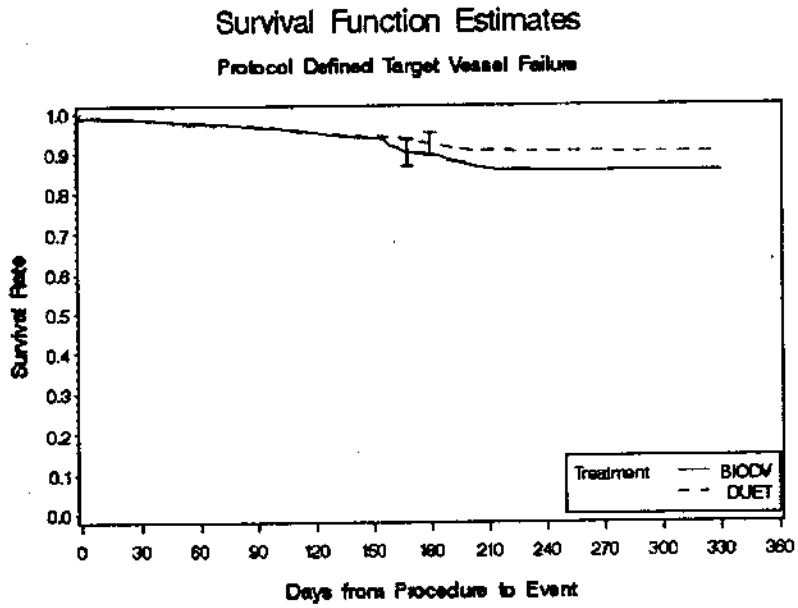
Table 6: Principal Effectiveness and Safety Results, All Patients Treated (N=621)

	BiodivYsio AS Group	ACS Duet Group	Difference (CI)
Effectiveness Measures:			
Technical Device Success	95.5% (296/310)	97.7% (301/308)	-2.2% (-5.1%,0.6%)
Clinical Device Success	94.8% (294/310)	96.4% (297/308)	-1.6% (-4.8%,1.6%)
Procedure Success	91.9% (285/310)	96.7% (298/308)	-4.8% (-8.4%, 1.2%)
TVF-Free (protocol) at 6 Months*	90.1%	92.2%	-2.1% (-6.6%, 2.3%)
TVF-Free (revised) at 6 months*	92.0%	92.9%	-0.9% (-5.0%, 3.3%)
TVR-Free at 6 Months*	91.3%	94.2%	-2.8% (-6.9%, 1.3%)
TLR-Free at 6 Months*	91.3%	94.8%	-3.5% (-7.4%, 5.1%)
%DS at 6 Months by QCA	33.3%	29.3%	4.0 (-0.9, 8.8)
Restenosis Rate	19.9% (29/1460)	20.1% (30/149)	-0.3% (-9.4%, 8.9%)
Restenosis Rate for Procedural Success	17.7% (24/135)	18.7% (27/144)	-1.0% (-10.0%,8.1%)
Safety Measures:			
In-Hospital Clin Events	1.6% (5/312)	3.2% (10/309)	-1.6 (-6.2, 1.8)
Out-Hospital Clin Events	15.4% (48/312)	11.0% (34/309)	4.4 (-1.5, 11.4)
(Sub)Acute Occlusions	0.0% (0/312)	0.6% (2/309)	-0.6 (3.8, 1.5)
Vascular Complications	0.3% (1/312)	1.3% (4/309)	-1.0 (-4.7, 1.5)
Bleeding Complications	0.3% (1/312)	0.6% (2/309)	-0.3 (-3.8, 2.0)

*Survival analysis is based on Kaplan Meier survival methods.
Numbers are % (numerator/denominator), mean, 1 SD, CI = 95% confidence interval.
Odds ratio = BiodivYsio™ AS/Duet group
Difference = BiodivYsio™ AS – Duet
KM Difference = S_{Biodiv}/S_{Duet} $SE_{diff} = sqrt(SE_{Biodiv}^2 + SE_{Duet}^2)$ and CI = diff $\pm$ 1.96SE_{diff}
Technical Device Success—Intended stent successfully implanted as first stent with a ≥ 20% reduction in percent diameter stenosis of the target lesion and a ≤ 50% final diameter stenosis.
Clinical Device Success—Technical device success and no MACE events through discharge
Procedural Success—≥ 20% reduction in percent stenosis of the target lesion and a ≤ 50% final diameter stenosis using the assigned treatment stent alone.
TVF (per protocol) - target vessel failure is a composite of death, MI, and ischemia-driven revascularization (PTCA or CABG) to the target vessel.
TVF (revised)—target vessel failure as revised is a composite of death, recurrent MI, emergent CABG, and ischemia driven revascularization (PTCA or CABG) to the target vessel.
Clinical Events—MACE (death, non-fatal MI, and CABG or PTCA at the target vessel or target lesion), (sub)acute occlusions or bleeding and vascular complications as determined by the Clinical Events Committee.
DS—diameter stenosis compared to the reference vessel diameter
Restenosis Rate—percent diameter stenosis > 50% at 6 months follow-up by QCA when compared to the reference vessel lumen diameter.
Restenosis Rate for Procedural Success—restenosis rate in the angiographic cohort who achieved procedural success.
QCA—quantitative coronary angiography
Bleeding Complications—bleeding requiring transfusion or prolonged hospitalization
Vascular Complications—events requiring surgery
CABG—Coronary Artery Bypass Graft
PTCA—Percutaneous Transluminal Coronary Angioplasty

10.10 Survival Analysis

Figure 1: Kaplan Meier Estimate for Freedom From Target Vessel Failure



	Days after Procedure							
	0	**7**	**14**	**30**	**90**	**180**	**248**	**273**
Biodivysio AS								
# At risk	313	310	310	310	309	301	279	263
# Events	3	3	3	4	11	31	45	45
% Survived	99.0%	99.0%	99.0%	98.7%	96.5%	90.1%	85.5%	85.5%
SE	0.006	0.006	0.006	0.006	0.010	0.017	0.020	0.020
ACS Duet								
# At risk	309	305	305	305	305	299	284	278
# Events	4	4	4	4	9	24	29	30
% Survived	98.7%	98.7%	98.7%	98.7%	97.1%	92.2%	90.6%	90.3%
SE	0.006	0.006	0.006	0.006	0.010	0.015	0.017	0.017

Tests Between Groups

Test	**Chi-Square**	**DF**	**P-value**
Log-Rank	3.0923	1	0.0787
Wilcoxon	2.9263	1	0.0871

11. Conclusions Drawn From Studies

11.1 Safety

The preclinical studies conducted on the 15 mm Bio*divYsio*™AS included biocompatibility, sterilization and *in-vitro* bench testing (stent material), specifications and conformance, stent integrity, stent and delivery system performance, package integrity and shelf life. The results of biocompatibility testing demonstrated that the stent is acceptable for long-term (implant, circulating blood) invasive use in the cardiovascular system. The results of *in-vitro* bench testing demonstrated that the performance characteristics of the stent and its delivery system met product specifications and that they are safe for clinical use.

11.2 Effectiveness

The results of the DISTINCT clinical study indicated that the primary and secondary objectives were met in that the Bio*divYsio*™ AS has comparable rates with the control system TVF at 180 days and with binary restenosis. The MACE data between the two groups are similar.

12. Panel Recommendation

Pursuant to Section 515 (c) (2) of the Federal Food, Drug and Cosmetic Act as Amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA Advisory Panel, for review and recommendation because the information in the PMA substantially duplicated information previously reviewed by this panel.

13. FDA Decision

FDA issued an approval order on September 29, 2000. The applicant's manufacturing facility was inspected and was found to be in compliance with the device Quality System Regulations, 21CFR Part 820.

14. Approval Specifications

- Instructions for Use (see the labeling)
- Hazards for health from use of the device: see indications, contraindications, warnings, precautions and adverse events labeling.