



P970035

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 23 1997

Dr. Azin Parhizgar
Director of Regulatory and Clinical Affairs
Arterial Vascular Engineering, Inc.
3576 Unocal Place
Santa Rosa, CA 95403

Re: P970035
AVE Micro Stent™ II Over-the-Wire Coronary Stent System and
AVE GFX™ Over-the-Wire Coronary Stent System
Filed: August 5, 1997
Amended: August 13, September 30; October 6, November 6,
November 21, December 18 and December 22, 1997

Dear Dr. Parhizgar:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the AVE Micro Stent™ II Over-the-Wire Coronary Stent System and the AVE GFX™ Over-the-Wire Coronary Stent System. The devices are indicated for use in patients eligible for balloon angioplasty with symptomatic ischemic disease due to discrete de novo lesions in native coronary arteries (length \leq 30 mm) with a reference vessel diameter of 3.0 mm to 4.0 mm. Stenting is intended to improve coronary luminal diameter (see Individualization of Treatment). Long term outcome (beyond 6 months) for this permanent implant is unknown at present.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the

training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the postapproval requirements in the enclosure, the postapproval reports must include the following information:

Further characterization of long-term safety and effectiveness by following for 5 years from implant at least 250 of the 330 patients implanted with the AVE Micro Stent™ II, and at least 160 of the 210 patients implanted with the GFX™ stent in the SMART Trial.

The protocol for this study and study timelines will be submitted to the Agency for review within 30 days of approval. The final protocol will be developed interactively with the FDA review team.

Summary reports will be submitted to the Agency annually and a final report at the end of the study.

Expiration dating for this device has been established and approved at 1 year for the AVE Micro Stent™ II and the AVE GFX™ Over-the-Wire Coronary Stent Systems. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

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PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

In addition under section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the act (21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

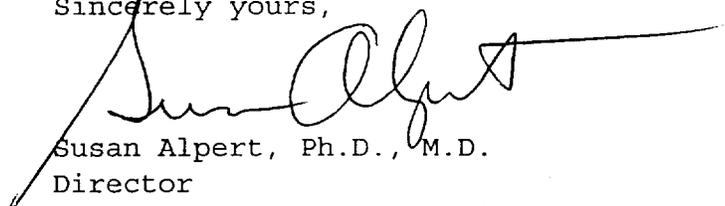
If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)). Pursuant to 21 CFR § 821.20(d), FDA will be adding coronary stents to these lists by publishing a notice in the FEDERAL REGISTER announcing that FDA believes that this device is subject to tracking under section 519(e)(1). This notice will also solicit public comments on FDA's determination.

If you have any questions concerning this approval order, please contact H. Semih Oktay, Ph.D., at (301) 443-8243.

Sincerely yours,



Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effectuated" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effectuated." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

- (1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).
- (2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:
 - (a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

- (b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

- (1) A mixup of the device or its labeling with another article.
- (2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and
 - (a) has not been addressed by the device's labeling or
 - (b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.
- (3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

- (1) may have caused or contributed to a death or serious injury or
- (2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 240
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

AVE Micro Stent™ II and GFX™ Coronary Stent Systems SUMMARY OF SAFETY AND EFFECTIVENESS DATA

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AVE Micro Stent™ II and GFX™ Coronary Stent Systems

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1. GENERAL INFORMATION

Device Generic Name: Intravascular Coronary Stent

Device Trade Name: AVE Micro Stent™ II Over-the-wire Coronary Stent System
..... AVE GFX™ Over-the-wire Coronary Stent System

Applicant's Name and Address: Arterial Vascular Engineering Incorporated
3576 Unocal Place
Santa Rosa, California 95043

PMA Application Number: P970035

Date of Panel Recommendation: not applicable

Date of Notice of Approval to the Applicant: December 23, 1997

2. INDICATIONS

The AVE Micro Stent™ II and GFX™ Over-the-wire Coronary Stent Systems are indicated for use in patients eligible for balloon angioplasty with symptomatic ischemic disease due to discrete *de novo* lesions in native coronary arteries (length \leq 30 mm) with a reference vessel diameter of 3.0 mm to 4.0 mm. Stenting is intended to improve coronary luminal diameter. (see Section 11.4, Labeling). Long term outcome (beyond 6 months) for this permanent implant is unknown at present.

3. CONTRAINDICATIONS

The AVE Micro Stent™ II and GFX™ Over-the-wire Coronary Stent Systems are contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon.

4. WARNINGS AND PRECAUTIONS

4.1 Warnings

- Since the use of this device carries the associated risk of subacute thrombosis, vascular complications and/or bleeding events, judicious selection of patients is necessary.
- Patients allergic to 316L stainless steel may suffer an allergic reaction to this implant.

4.2 PRECAUTIONS

- Only physicians who have received appropriate training should perform implantation of the stent.

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- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent restenosis may require re-dilatation of the arterial segment containing the stent. When multiple stents are required, stent materials should be of similar composition. The long-term outcome following such repeat dilatation of the coronary stents

4.2.1 Stent Handling - Precautions

- **For single use only.** Do not resterilize or reuse. Note product “Use By” date.
- The AVE Micro Stent™ II and GFX™ Over-the-wire Coronary Stent Systems are designed for use as a unit. The Stent is not to be removed from its delivery balloon. The AVE Micro Stent™ II and GFX™ Over-the-wire Coronary Stent Systems are not designed to be crimped onto another balloon. Removing the stent from its delivery balloon may damage the stent and/or lead to stent embolization.
- Special care must be taken not to handle or in any way disrupt the stent position on the delivery device. This is most important during catheter removal from packaging, placement over guidewire and advancement through hemostasis valve adapter and guiding catheter hub.
- Excessive manipulation, e.g., rolling the mounted stent may cause dislodgment of the stent from the delivery balloon.
- Use only the appropriate balloon inflation media. Do not use air or any gas medium to inflate the balloon as it may cause uneven expansion and difficulty in deployment of the stent.

4.2.2 Stent Placement – Precautions

- **Do not prepare or pre-inflate the balloon prior to stent deployment**, other than as directed. Use balloon purging technique described in the Instructions for Use.
- Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel requiring additional intervention (e.g., CABG, further dilation, placement of additional stents, or other).
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the proximal lesion. Stenting in this order obviates the need to cross the proximal stent when placing the distal stent and reduces the chances for dislodging the proximal stent.
- Do not expand the stent if it is not properly positioned in the vessel. (see Stent/System Removal-Precautions)
- Placement of the stent has the potential to compromise side branch patency.
- Balloon pressures should be monitored during inflation. **Do not exceed rated burst pressure indicated on product label.** (See Balloon Inflated Diameter dimensions in Table 10/Table 11.) Use of pressures higher than those specified on product label may result in a ruptured balloon and potential intimal damage and dissection.
- **Do not attempt to pull an unexpanded stent back through the guiding catheter, as dislodgment of the stent from the balloon may occur.** (see Stent/System Removal-Precautions)

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

4.2.3 Stent/System Removal- Precautions

Should unusual resistance be felt **at any time**, either during lesion access or during the removal of the Stent Delivery System post-stent implantation, the Stent Delivery System and the guiding catheter **should be removed as a single unit**. This must be done under direct visualization with fluoroscopy.

When removing the Stent Delivery System as a single unit:

- **Do not pull the Stent Delivery System into the guiding catheter.** Maintain guidewire placement across the lesion and carefully pull back the Stent Delivery System until the proximal balloon marker of the Stent Delivery System is aligned with the distal tip of the guiding catheter.
- The guiding catheter and Stent Delivery System should be carefully removed from the coronary artery as a single unit.
- The system should be pulled back into the descending aorta toward the arterial sheath. As the distal end of the guiding catheter enters into the arterial sheath, the catheter will straighten allowing safe withdrawal of the Stent Delivery System into the guiding catheter and the subsequent removal of the Stent Delivery System and the guiding catheter from the arterial sheath.
- Failure to follow these steps and/or applying excessive force to the Stent Delivery System can potentially result in loss or damage to the stent or Stent Delivery System components such as the balloon.

4.2.4 Post-Stent Placement – Precautions

- Care must be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) or a coronary guidewire, or a balloon catheter, to avoid disrupting the stent geometry.
- Do not perform Magnetic Resonance Imaging (MRI) scan on patients post-stent implantation until the stent has been completely endothelialized (eight weeks) to minimize the potential for migration. The stent may cause artifacts in MRI scans due to distortion of the magnetic field.

5. DEVICE DESCRIPTION

The AVE Micro Stent™ II and GFX™ Over-the-Wire Coronary Stent Systems, hereafter called the Micro Stent™ II and GFX™ Stent Systems, are comprised of two components: the implantable stent and the delivery system. The stent is fabricated from 316L stainless steel wire and derived from individual segments which are laser welded together to create the various lengths. These segments are created from a single ring formed into a repeating pattern of crowns and struts. The Micro Stent™ II is comprised of four crowns and a 3mm-segment configuration with lengths ≤39-mm. All Micro Stent™ II wires have circular cross sections.

The GFX™ Stent is comprised of six crowns and a 2-mm segment configuration with lengths ≤30-mm. The GFX™ Stent wires have ellipso-rectangular cross sections.

The stents are pre-mounted on an Over-The Wire (OTW) percutaneous transluminal coronary angioplasty (PTCA) catheter using a sheathless design. A polyethylene balloon mounted on the

distal end of the catheter provides a platform for mounting, delivering and deploying the stent. The shaft of the delivery system is coaxial over the distal section and transitions into proximal multi-lumen tubing. A guidewire lumen extends through the entire length of the catheter and is compatible with a 0.014-inch guidewire. A second lumen also extends the entire length of the catheter and is used for inflation and deflation of the balloon. The stent delivery system has two radiopaque (gold) markers embedded in the inner shaft distal and proximal to the stent. The markers are visible under fluoroscopy. The device is supplied sterile, for single use only.

Tables 1 and 2 provide the product labeling specifications for the Micro Stent™ II and GFX™ Stent Systems.

Table 1. Device Specifications - Micro Stent™ II

Stent Diameter (mm)	Stent Lengths (mm)	Minimum Guiding Catheter Inner Diameter* (inches)	Stent Deployment Pressure (ATM)	Rated Burst Pressure (ATM)	Stent Free Area (%)
3.0	6, 9, 12, 15, 18, 24	0.072	9	9	83
3.0	30	0.76	9	9	83
3.5	6, 9, 12, 15, 18, 24	0.072	9	9	85
3.5	30	0.76	9	9	85
4.0	6, 9, 12, 15, 18, 24, 30	0.076	9	9	87

❖ See individual manufacture specifications for (Fr.) equivalent

Table 2. Device Specifications- GFX™

Stent Diameter (mm)	Stent Lengths (mm)	Minimum Guiding Catheter Inner Diameter* (inches)	Stent Deployment Pressure (ATM)	Rated Burst Pressure (ATM)	Stent Free Area (%)
3.0	8,12,18,24	0.064	9	9	77
3.0	30	0.072	9	9	77
3.5	8,12,18,24	0.064	9	9	80
3.5	30	0.072	9	9	80
4.0	8,12,18,24,30	0.072	9	9	83

❖ See individual manufacture specifications for (Fr.) equivalent

6. ALTERNATIVE PRACTICES AND PROCEDURES

Patients with early coronary artery disease receive exercise, diet and drug therapy. If the disease progresses, PTCA, coronary artery bypass graft (CABG) surgery or stenting with other commercially available stents may be performed.

7. MARKETING HISTORY

The Micro Stent™ II and GFX™ Stent Systems are legally marketed internationally under the following trade names:

AVE Micro Stent™ II Coronary Stent System

AVE GFX™ Coronary Stent System

The specific countries are as follows:

Argentina	Finland	Korea	South Africa
Australia	France	Luxembourg	Spain
Austria	Germany	Malaysia	Sweden
Belgium	Greece	Mexico	Switzerland
Brazil	Hong Kong	Netherlands	Taiwan
Bulgaria	Hungary	New Zealand	Thailand
Chile	Iceland	Norway	Turkey
China	India	Pakistan	United Kingdom
Colombia	Ireland	Poland	Uruguay
Czech Republic	Israel	Portugal	Venezuela
Denmark	Italy	Saudi Arabia	
Egypt	Japan	Singapore	

The Micro Stent™ II and GFX™ Stent Systems have not been withdrawn from marketing for any reason relating to the safety and/or the effectiveness of the device.

8. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A total of 1084 patients were enrolled in three multi-center clinical studies to evaluate the safety and effectiveness of the balloon expandable, Micro Stent® II and GFX™ Stent Systems for treatment of symptomatic coronary artery disease. Of these, 543 received the Micro Stent® II, 210 received the GFX™ Stent, and 331 received the Johnson and Johnson Interventional Systems Palmaz-Schatz® Stent while participating in the SMART Randomized Clinical Study. These patients form the basis of the observed events reported. The GFX™ Stent Study enrolled two hundred ten (210) patients in a non-randomized, multi-center study. These patients form the basis for the observed events reported.

Table 3. Summary of Clinical Study Patient Enrollment (n=1084)

	AVE Stent System	Palmaz-Schatz® Coronary Stent- Control	Patient Totals
SMART Randomized Study	Micro Stent® II = 330	331	661
Feasibility Study	Micro Stent® II = 213	NA	213
GFX Study	GFX™ Stent = 210	NA	210
Patient Totals	753	331	1084

8.1 Observed Adverse Events

8.1.1 Randomized Clinical Study and Feasibility Study

A total of 120 of 543 patients (22.1%) who received the Micro Stent® II experienced one or more adverse events during the first 6 months of follow-up compared to 59 of 331 control patients (17.7%).

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Table 4. Adverse Events during the First 6 Months
 % [\pm 95 % Confidence Interval] Number/Denominator; (n=874)

SMART STUDY		
	Micro Stent® II (n=543)	Palmaz-Schatz® (n=331)
Death Total	1.7% [0.8%,3.1%] (9/543)	0.6% [0.1%,2.2%] (2/331)
Early (in-hospital)	0.6% [0.1%,1.6%] (3/543)	0.3% [0.0%,1.7%] (1/331)
Out-of -hospital	1.1% [0.4%,2.4%] (6/543)	0.3% [0.0%,1.7%] (1/331)
Q-wave MI Total	0.7% [0.2%,1.9%] (4/543)	0.6% [0.1%,2.2%] (2/331)
Early (in-hospital)	0.6% [0.1%,1.6%] (3/543)	0.6% [0.1%,2.2%] (2/331)
Out-of -hospital	0.2% [0.0%,1.0%] (1/543)	0.0% [0.0%,0.9%] (0/331)
Non-Q-wave Total	4.6% [3.0%,6.7%] (25/543)	3.9% [2.1%,6.6%] (13/331)
Early (in-hospital)	3.9% [2.4%,5.9%] (21/543)	3.3% [1.7%,5.9%] (11/331)
Out-of -hospital	0.7% [0.2%,1.9%] (4/543)	0.6% [0.1%,2.2%] (2/331)
CABG Total	3.9% [2.4%,5.9%] (21/543)	2.4% [1.0%,4.7%] (8/331)
Early (in-hospital)	1.3% [0.5%,2.6%] (7/543)	1.2% [0.3%,3.1%] (4/331)
Out-of -hospital	2.6% [1.4%,4.3%] (14/543)	1.2% [0.3%,3.1%] (4/331)
Stent Thrombosis Total	0.6% [0.1%,1.6%] (3/543)	0.6% [0.1%,2.2%] (2/331)
Early (in-hospital)	0.6% [0.1%,1.6%] (3/543)	0.3% [0.0%,1.7%] (1/331)
Out-of -hospital	0.0% [0.0%,0.6%] (0/543)	0.3% [0.0%,1.7%] (1/331)
Bleeding Requiring Transfusion-Procedural	1.8% [0.9%,3.4%] (10/543)	1.5% [0.5%,3.5%] (5/331)
Vascular Complications	5.5% [3.8%,7.8%] (30/543)	3.3% [1.7%,5.9%] (11/331)
Cerebrovascular Accidents	0.7% [0.2%,1.9%] (4/543)	0.0% [0.0%,0.9%] (0/331)
Stent Delivery Failure	2.5% [1.3%,4.1%] (14/543)	4.8% [2.8%,7.7%] (16/331)

NOTE: * In cases where a patient experienced both an in-hospital event and an out-of-hospital event they are counted once in each group. They are counted only once in the event total. Hence, the sum of the in-hospital event rate and the out-of-hospital event rate may not equal the total event rate.

Adverse event rates for the randomized patients in the SMART Study (n=661) were not statistically different (p>0.01).

A total of 9 of the 543 patients who received the Micro Stent® II died during the clinical study. The 3 in-hospital deaths included one myocardial infarction at 192 hours after the stent placement and cardiac arrests occurring at 9 and 48 hours after stenting. The 6 out-of-hospital deaths occurred between 47 days and 244 days after stenting and were due to myocardial infarction (n=2), cardiac arrest (n=3), and pneumonia (n=1).

Stent thrombosis occurred in 0.6% of the patients who received the Micro Stent® II. The incidence of vascular complications after stent placement was 5.5% (30/ 543) of the patients. The rate for procedural bleeding requiring transfusion was 1.8% (10/ 543) of the patients.

Initial delivery failure occurred in 2.5% (14/543) of the patients as follows: operator was unable to deliver first stent (n=7) and failure to deliver the assigned stent (n=7).

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8.1.2 GFX™ Study

A total of 14 of 210 patients (6.6%) who received the GFX™ Stent experienced one or more adverse events during the first 30 days of follow-up compared to 53 of 331 control patients (16%).

Table 5. Adverse Events at 30 Days
% [\pm 95 % Confidence Interval] Number/Denominator; (n=541)

	GFX Stent™ N=210	Palmaz-Schatz® N=331
Death	0.5% [0.0%,2.6%] 1/210	0.3% [0.0%,1.7%] 1/331
In-Hospital	0.5% [0.0%,2.6%] 1/210	0.3% [0.0%,1.7%] 1/331
Out-of-hospital	0.0% [0.0%,1.4%] 0/210	0.0% [0.0%,0.9%] 0/331
Q-wave MI	0.0% [0.0%,1.4%] 0/210	0.6% [0.1%,2.2%] 2/331
In-Hospital	0.0% [0.0%,1.4%] 0/210	0.6% [0.1%,2.2%] 2/331
Out-of-hospital	0.0% [0.0%,1.4%] 0/210	0.0% [0.0%,0.9%] 0/331
Non Q-wave MI	2.9% [1.1%,6.1%] 6/210	3.9% [2.1%,6.6%] 13/331
In-Hospital	0.5% [0.0%,2.6%] 1/210	0.6% [0.1%,2.2%] 2/331
Out-of-hospital	2.4% [0.8%,5.5%] 5/210	3.3% [1.7%,5.9%] 11/331
CABG	0.0% [0.0%,1.4%] 0/210	1.2% [0.3%,3.1%] 4/331
In-Hospital	0.0% [0.0%,1.4%] 0/210	1.2% [0.3%,3.1%] 4/331
Out-of-hospital	0.0% [0.0%,1.4%] 0/210	0.0% [0.0%,0.9%] 0/331
Stent thrombosis	1.0% [0.1%,3.4%] 2/210	0.6% [0.1%,2.2%] 2/331
Bleeding (procedural transfusion)	0.0% [0.0%,1.4%] 0/210	1.5% [0.5%,3.5%] 5/331
Stroke	0.0% [0.0%,1.4%] 0/210	0.0% [0.0%,0.9%] 0/331
Vascular (local) complications	0.5% [0.0%,2.6%] 1/210	3.0% [1.5%,5.5%] 10/331
Stent Failures	1.9% [0.5%, 4.8%] 4/210	4.8% [2.8%,7.7%] 16/331

A total of 1 of the 210 patients who received the GFX™ Stent died during the clinical study. The in-hospital death occurred 21 days after stenting and was due to cardiac arrest (n=1).

Stent thrombosis occurred in 1.0% of the patients who received the GFX™ Stent. The incidence of vascular complications of the stent placement was 0.5% (1/ 210) of the patients. The rate for procedural bleeding requiring transfusion was 0.0%.

Initial delivery failure occurred in 1.9% (4/ 210) of the patients as follows: operator was unable to deliver first stent (n=2), failure to deliver second stent (n=1), and failure to deliver third stent (n=1).

8.2 Potential Adverse Events

Adverse events (in alphabetical order) that may be associated with the use of a coronary stent in native coronary arteries (including those listed in Tables 4 and 5) are:

Acute myocardial infarction	Arrhythmia's, including VF and VT
Death	Dissection
Drug reactions to antiplatelet agents/ contrast medium	Emboli, distal (air, tissue or thrombotic emboli)
Emergent Coronary Artery Bypass Surgery	Hemorrhage, requiring transfusion
Hypotension/Hypertension	Infection and pain at the vascular access site

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Ischemia, myocardial
Pseudoaneurysm, femoral
Spasm
Stent thrombosis/occlusion
Total occlusion of coronary artery

Perforation
Restenosis of stented segment
Stent embolization
Stroke/Cerebrovascular Accidents

9. SUMMARY OF PRECLINICAL STUDIES

9.1 Biocompatibility Testing

Biocompatibility testing was conducted in accordance with ISO 10993-1, and the Tripartite Biocompatibility Guidance for Medical Devices. The testing included cytotoxicity, hemolysis, acute systemic toxicity, irritation, sensitization, material mediated pyrogenicity, complement, coagulation, and thromboresistance. The Micro Stent® II and GFX™ Stent Systems passed all applicable biocompatibility tests.

The genotoxicity, mutagenicity, carcinogenicity, subchronic toxicity, biodegradation and developmental/reproductive tests were not conducted due to the historical use of 316L stainless steel for implantation throughout the body, and because the delivery system is not a permanent implant (and thus exempt from these particular tests per ISO).

9.2 Sterilization Testing

Sterilization of the Micro Stent® II and GFX™ Stent Systems, and the packaging were validated in accordance with the AAMI Guideline for Electron Beam Radiation Sterilization of Medical Devices, Method 1, ANSI/AAMI ST31-1990. This testing demonstrated that the Micro Stent® II and GFX™ Stent Systems were sterilized according to the specified parameters and validated to have a SAL of 10^{-6} .

9.3 Animal Studies

In-vivo animal testing was conducted on the Micro Stent® II and GFX™ Stent Systems. Angiographic, pathologic and histologic assessments of the stents were conducted on a total of 52 stented vessel segments in 18 healthy male canines at a duration between one day and six months. The average lumen diameter of the stented vessel segment was largest at 2 weeks (3.3 ± 0.6 mm). The smallest average diameters were observed at 8 weeks after stent deployment (2.7 ± 0.4 mm, $P < 0.05$) with an increase again at 24 weeks (2.9 ± 0.6 mm). The overall data suggests that constrictive remodeling of the stented vessel segment occurs at 8 weeks in the animal model. Pathological and histological analyses demonstrated no gross abnormalities. There were no procedural complications, deaths or acute vessel closures.

The Micro Stent® II was used as a control against the GFX™ Stent in a separate study conducted in the iliac arteries of 13 New Zealand white rabbits. The study was designed to compare the 3 day and 28 day vascular/pathologic response of the two designs with the assertion that the two designs were similar enough to not require a study of patency rates. Eleven animals survived the 28 days necessary to obtain the data. The 3-day mural response, 28-day neointimal hyperplasia, 28-day remodeling response, and 28-day percent luminal narrowing were significantly lower for the GFX™ Stent, whereas, the 28-day proliferation was significantly higher. This increased proliferation was attributed to the increased surface area of the stent.

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9.4 In Vitro Bench Testing

In-Vitro bench testing was conducted on the Micro Stent® II and GFX™ Stent Systems according to the FDA Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices, May 1994, which not only specifies the tests to be performed, but also the number of devices/samples to be tested.

9.4.1 Stent Material Specification Conformance and Integrity Testing

9.4.1.1 Chemical Analysis

The Micro Stent® II and GFX™ Stent are fabricated from medical grade 316L stainless steel tubing, which conforms to ASTM F-138-92 Grade 2 and ISO 5832-1, in both the chemical analysis and the inclusion/impurity content. All materials met the specifications.

9.4.1.2 Yield Strength and Elongation

The tensile strength and elongation test was performed to determine the yield strength and percent elongation of the Micro Stent® II and GFX™ ring material. Five annealed rings were tested per ASTM method E8. The yield strength and elongation of the Micro Stent® II and the GFX™ Stent met the product specifications. The results of the testing are presented in Table 6.

Table 6. The Material Properties of 316L used in the Micro Stent® II and the GFX™ Stent

Description	Specification	N	Mean	K factor level	K factor	LTL
Yield	25,000 psi Min.	5	38.32 ksi	$\gamma = 0.90$ P = 0.95	3.400	38.1 ksi
Ultimate	70,000 psi Min.	5	82.51 ksi	$\gamma = 0.90$ P = 0.95	3.400	78.7 ksi
Elongation	40% Min.	5	53.44%	$\gamma = 0.90$ P = 0.95	3.400	41.95%

9.4.1.3 Corrosion

The corrosion test was conducted on non-welded and welded stent components to determine the susceptibility of the Micro Stent® II and the GFX™ Stent to corrosion and pitting. The test was conducted on two 4-mm stent segments per ASTM A 262-91 to meet ASTM F 138-92 specifications. The stent corrosion resistance met ASTM F 138-92, grade 2 specifications. No evidence of intergranular attack was visible under 30X magnification. Corrosion analysis of welded segments was performed on 92 samples. No evidence of preferential attack was observed on either welded or base metal regions.

9.4.1.4 Dimensions

The dimensional measurements of the stent were made under 40x magnification. Measurements (i.e., cross section, weld length and visual inspection) were made on 162 (of all sizes) Micro Stent® II and the GFX™ Stents (all sizes). The dimensional specifications were met in all cases. All units passed the visual inspection.

9.4.1.5 Stent-Free Area Percentage

The stent-free area percentage was found by subtracting the area of the stent from the total stented vessel area, and then divided by the total stented vessel area. The stent-free area percentage was calculated using a nominal round cross section dimensions. The metal to artery ratio (MAR) ranged between 12.9 to 17.2 percent for the Micro Stent® II and between 17 to

22.7 percent for the GFX™ Stent. These values of stent free area compared well with current commercially available stents, *i.e.*, they were within the same range.

9.4.1.6 Length Change

The length change test determined the percent shortening of the Micro Stent® II when expanded to the nominal diameter. The length changes ranged from 4 percent for a 3.0-mm stent, to 8 percent for a 3.5-mm stent, to a maximum of 12 percent for a 4.0-mm device. The GFX™ Stent showed a maximum of 9.7 percent decrease in length upon deployment. The length change of the Micro Stent® II and the GFX™ Stent was acceptable.

9.4.1.7 Uniformity of Expansion

The uniformity of expansion test measured the uniformity of the Micro Stent® II and the GFX™ Stent along their length after balloon expansion at 9 ATM. The outer diameter was then measured at 3 places via a snap gage and later averaged. All samples were within the specifications (± 0.381 -mm) of the labeled diameter when deployed at 9 ATM. Note that uniformity was defined as the mean outer diameter plus or minus the standard deviation.

9.4.1.8 Recoil

The recoil test determined the percent recoil of the stent after balloon expansion. The stent outer diameter was measured on six of each size stent using a snap gage with and without the expanded balloon in place. The stent internal diameter was determined incrementally using pin gages. The recoil of the Micro Stent® II and the GFX™ Stent met the product specifications.

9.4.1.9 Compression - Radial Strength (Pressure Vessel)

The pressure vessel compression test was used to determine the hoop strength of the Micro Stent® II and the GFX™ Stent. The stent is expanded inside a thin-walled balloon. Vacuum was then applied to the balloon radially compressing the stent. The results indicated that a vacuum in excess of 230 mmHg within the thin-walled balloon is necessary to create permanent deformation in the stent when deployed to nominal diameter. The results also indicated that the stent design met the $\geq 50\%$ inner diameter requirement after exposure to >500 mmHg. The radial (hoop) strength and irreversible deformation of the Micro Stent® II and the GFX™ Stent met the product specifications.

9.4.1.10 Accelerated Fatigue

The accelerated fatigue test was performed on both the Micro Stent® II and GFX™ Stent to determine fatigue in a physiologically simulated loading environment under accelerated conditions. The stents tested included 192 crowns. The pressure fluctuation used in this test (240 mm Hg range) was in excess of that experienced clinically. The long term radial fatigue testing results are shown in Table 7.

Table 7. Results From the Long Term Radial Accelerated Fatigue Testing

Samples	Cycles	Status	Results
12 - 6 mm MS II	420 Million	Complete	No Failures or Separations

The long term bending fatigue testing was performed on 32 samples of the Micro Stent® II with 128 weld points. All samples met the specifications (Table 8).

Table 8. Results From the Long Term Bending Fatigue Testing

Samples	Cycles	Status	Results
32 - 6 mm MS II	420 Million	Complete	No Failures or Separations

As for the GFX™ Stent, individual crown segments were fatigue tested to simulate the repetitive radial compression experienced in human coronary arteries. These tests were conducted on both welded and non-welded segments (as was the case in Micro Stent® II fatigue testing). Stent crown segments were manufactured according to standard production processes (including annealing, forming and electropolishing). Five hundred eighty-nine (589) stent segments (both the welded and non-welded) were tested at various displacements. The stents were cut horizontally through the end of the crown. Stents were then distended to an effective 4.0-mm diameter. For welded segments, the struts were trimmed from the adjacent segment leaving only the crown in place. The cut crowns were loaded into the fatigue jaws, and clamped into place. The resulting fatigue data were plotted in the typical S-N curve and statistically analyzed. Both the Micro Stent® II and GFX™ Stent met the 10 year accelerated fatigue resistance requirement of the product specifications.

9.4.1.11 Finite Element Analysis (FEA)

The FEA evaluated the structural integrity of the Micro Stent® II and GFX™ Stent. The simulation was a finite element analysis of the stent subjected to expected load conditions generated in coronary arteries. The analysis took into account radial pressures and bending forces at nominal balloon expansion, and ten-year radial contractive fatigue cycling for both models. The appropriate material properties and characteristics were entered into the model. The increases in the yield and ultimate tensile strengths were calculated by the model. The results from this model were used to construct a combined Goodman/Gerber diagram. The safety factors were about 1.5 to 2 for the Micro Stent® II and 4 for the GFX™ Stent. The stents met the FEA requirement of the product specifications.

9.4.1.12 Weld Tensile Strength

The weld tensile strength was tested on both the Micro Stent® II and the GFX™ Stent. The weld tensile breaking load was measured on a total of 104 welded segments from the Micro Stent® II and 49 segments from the GFX™ Stent. The results are shown in Table 9.

Table 9. Weld Tensile Strength Test Results for the Micro Stent™ II (a) And the GFX™ Stent (b)

Weld Tensiles	
Acceptance Range (lbs.Min)	2.0
Mean (lbs.)	7.938
Standard Deviation (lbs.)	0.374
Observations	104
K factor $\gamma = 0.99, P = 0.95$	2.269
Lower Tolerance Limit (lbs.)	7.089

(a)

Weld Tensiles	
Acceptance Range (lbs.Min)	2.0
Mean (lbs.)	4.406
Standard Deviation (lbs.)	0.334
Observations	49
K factor $\gamma = 0.99, P = 0.95$	2.313
Lower Tolerance Limit (lbs.)	3.633

(b)

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9.4.1.13 Magnetic Resonance Imaging (MRI)

The Micro Stent® II and the GFX™ Stent are fabricated from 316L stainless steel material which has a high nickel content that helps to stabilize iron in a nonmagnetic state thereby diminishing magnetic susceptibility. Based on tests performed on 4-mm long stent segments, there were no distortions or artifacts noted in 1.5 Tesla MRI scans. The Micro Stent® II and the GFX™ Stent are considered MRI compatible.

9.4.2 Stent and Delivery System Testing:

The OTW Delivery System is identical for both Micro Stent® II and the GFX™ Stent with only minor differences in the balloon diameter. The following tests were conducted on both models to evaluate performance characteristics and safety of the stent/catheter system:

- Delivery System Profiles and Lengths (dimensional analysis)
- Crossing Profile Test
- Catheter Bend Integrity Test
- Bond strength (balloon and catheter)
- Material Analysis
- Inflation and Deflation Times Test
- Balloon Rated Burst and Compliance Test

All test results indicated that the devices/samples met the design specifications. The results of the Balloon Rated Burst and Compliance Test are communicated to the user in the device labeling as a table. Tables 10 and 11 will appear in the labeling for the GFX™ Stent and Micro Stent® II.

Table 10. Stent Diameter (mm) at Deployment Pressure (ATM) Compliance Chart

AVE GFX™ Over-the-wire Stent System						
Stent/ Balloon Diameter (mm)			Nominal			
	7 ATM	8 ATM	9 ATM†	10* ATM	11* ATM	12* ATM
3.0	2.8	2.9	3.0	3.1	3.1	3.2
3.5	3.3	3.4	3.5	3.6	3.7	3.7
4.0	3.8	3.9	4.0	4.1	4.2	4.3

* Beyond Rated Burst Pressure † Rated burst pressure

Table 11. Stent Diameter (mm) at Deployment Pressure (ATM) Compliance Chart

AVE Micro Stent® II Over-the-wire Stent System						
Stent/ Balloon Diameter (mm)			Nominal			
	7 ATM	8 ATM	9 ATM†	10* ATM	11* ATM	12* ATM
3.0	2.8	2.9	3.0	3.1	3.1	3.2
3.5	3.2	3.4	3.5	3.6	3.7	3.8
4.0	3.8	3.9	4.0	4.1	4.2	4.3

* Beyond Rated Burst Pressure † Rated burst pressure

9.4.3 Package Integrity Testing:

Packaged devices were sterilized and then exposed to a transportation simulation. The boxed test samples were prepared, shipped, tested at their destination per ASTM D 4169, then returned to AVE for post-test inspections. Only large (i.e., quantity 24), completely full, shipper boxes were used for this test. The samples all passed.

9.4.4 Shelf-Life (Aging) Testing:

The test protocol required the packaged devices to first undergo the package integrity test protocol. The test units were then exposed to environmental aging conditions including temperature and relative humidity and then tested for functional performance characteristics in addition to the package integrity tests. The accelerated aging process was performed at a temperature of 55°C which correlates to an ambient base of 22°C when an acceleration factor of 2.0 is used in accordance with "Accelerated Aging of Packaging: Considerations, Suggestions, and Use in Expiration Date Verification", by R. Reich, *et al.* Once processed, the samples were tested and evaluated per routine manufacturing methods. The results demonstrated that specifications/performance of the device will be maintained well beyond the labeled shelf life claim of one year and normal sterility irradiation exposure.

10. SUMMARY OF CLINICAL STUDIES

10.1 Objectives

Six hundred and sixty-one (661) patients were treated at forty (40) North American investigational sites in the Study of Micro-Stent's Ability to Limit Restenosis Trial (SMART), a multi-center, randomized, prospective controlled clinical study (RCT), to evaluate the safety and effectiveness of the Micro Stent® II (n=330) compared to the Palmaz-Schatz® (n=331) stent in treating *de novo* and restenotic lesions in the native coronary arteries. A separate non-randomized feasibility study (n=213) was conducted prior to beginning the randomized study. The primary end-point was defined as six-month need for Target Lesion Revascularization (TLR)¹.

The GFX™ Stent Study enrolled a total of 210 patients. The Palmaz-Schatz® Stent (n=331) was used as a retrospective control. The primary end point of the GFX™ Stent Study was defined as 30-day acute major events and success rates.

A clinical events committee blinded to the treatment assignment adjudicated all major clinical events and TLR.

10.2 Study Design

Eligibility was determined by the presence of angina or positive functional study (Exercise Treadmill Test). Patients were identified for elective stenting of *de novo* or restenotic lesions in native coronary arteries having vessel diameter between 3.0 mm and 4.0 mm with a lesion length of ≤ 30 mm, which could be covered by an appropriate length Micro Stent® II (i.e., 6, 15 or 30 mm), or a combination thereof, or a GFX™ Stent (i.e., 8, 18 or 30 mm), or a combination thereof. These patients underwent balloon angioplasty (1:1 balloon to artery ratio) after which a stent delivery system of the appropriate size was selected and deployed in the native coronary artery. Post deployment dilatation was performed utilizing a high-pressure balloon having a 1:1 balloon to artery ratio to obtain optimal stent apposition.

The anticoagulation regimen administered to 96.8% of the SMART RCT patients was 325 mg/day of uncoated, water-soluble aspirin for at least 6 months and ticlopidine 250mg twice a day for at least 14 days to 84% of the patients. At the discretion of the investigator, alternative

¹ TLR is defined as a clinically driven repeat revascularization of a target lesion that was angiographically narrowed. The definition of "clinically driven" included a positive functional ischemia study, resting ischemia ECG changes in a distribution consistent with the target vessel, or ischemic symptoms and an angiographic minimal lumen diameter stenosis ≥ 50% by quantitative coronary angiography (QCA); revascularization of a target lesion with diameter stenosis ≥ 70% by QCA without either angina or a positive functional study was also considered clinically driven.

therapy was allowed for non-optimal results, which were defined as > 30 mm stents implanted, >10% residual stenosis, any residual dissection, TIMI flow grade 0-1, or the presence of thrombus.

Clinical follow-up intervals for all treated SMART RCT patients were 30 days, 45 days, 6 months and 9 months. Follow-up for the GFX™ Stent Study patients was 30 days. A subset of patients underwent angiographic follow-up at 6 months for the SMART RCT. The study randomization was successful, within the SMART RCT, as both treatment groups were demographically equivalent. All treated randomized and non-randomized study patients were included in the intent-to-treat effectiveness analysis.

10.3 Gender Bias

To determine whether gender bias had occurred during the clinical studies, the ratio of women to men treated in the Micro Stent® II and GFX™ Stent groups was compared to that of the control group. There were no significant baseline differences in patient characteristics between the groups in either of the studies. This includes percent of males and females, age, incidence of diabetes, and hypertension. Statistical analysis of the clinical data did not show an association between gender and the primary or secondary clinical outcomes.

10.4 The SMART Study

10.4.1 Description of Patients

There were no major baseline differences in patient characteristics between the Micro Stent® II and Palmaz-Schatz® Stent groups, as seen in Table 12. The mean age of the pooled population was 64 ± 11 years and 70% of the population was male. Eighteen percent of the pooled population had diabetes mellitus, 58% had hypertension requiring treatment, and 32% had hyperlipidemia requiring medical intervention. Previous cardiovascular events included myocardial infarction in 29% of patients and 67% of patients had Canadian Cardiovascular Society (CCS) Class III or IV angina. The Micro Stent® II group did have a higher percentage of prior CABG (Micro Stent® II = 10% vs. Palmaz-Schatz® Stent = 5%, 95% CI = [0.6%, 8.5%]). Baseline angiography did not reveal any major differences between the two groups. Seventy-one percent of patients had single vessel disease, and the mean left ventricular ejection fraction was 57 ± 11%. There were no baseline differences in lesion characteristics between the two groups. The mean reference vessel diameter for all patients was 2.93 ± 0.51 mm while the minimum lumen diameter was 1.04 ± 0.40 mm. The baseline percent diameter stenosis was 64 ± 13%. Lesion length was 11.8 ± 6.3 mm and the majority of stents were placed in the LAD (44%), followed by the RCA (34%) and circumflex (22%) arteries.

Table 12. Patient Demographics

	Micro Stent® II	Palmaz-Schatz® Stent	95% CI of Difference
Number Treated	330	331	
% Receiving Assigned Stent	97.0	95.2	
% Male	69	70	-8.3, 5.7
% Diabetic	19	17	-4.3, 7.4
% Hypertension	58	58	-7.2, 7.9
% Hyperlipidemia	34	31	-4.5, 9.8
Age (yr.)	63 ± 11	64 ± 11	-2.5, 0.9
Reference Vessel Diameter (mm)	2.93 ± 0.54 (320)	2.93 ± 0.47 (320)	-0.08, 0.08
% Diameter Stenosis pre Procedure	65 ± 13 (322)	64 ± 13 (320)	-1.1, 3.0
Minimum Luminal Diameter (mm) pre Procedure	1.02 ± 0.40 (322)	1.06 ± 0.39 (320)	-0.10, 0.03

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10.4.2 Acute Procedural Results

Stenting demonstrated early safety and effectiveness in both groups. Acute procedural success (% diameter stenosis $\leq 50\%$ and no death, nonfatal myocardial infarction, CABG or repeat PTCA) was nearly identical, and there were no differences in lesion success or device success between the two groups. Post-stenting, the Micro Stent® II group had a slightly larger in-stent minimal lumen diameter so that the post-procedure in-stent percent diameter stenosis was smaller. Table 13 presents the principal effectiveness and safety results for the SMART study.

Table 13. Principal Effectiveness and Safety Results - SMART Study
Micro Stent® II (Randomized Control Study) vs. Palmaz-Schatz® Stent; (N=661)

Efficacy Measures	AVE Micro Stent II™ (N=330)	Palmaz-Schatz® (N=331)	Difference [95% C.I.]
Device Success by QCA	97.8% [95.5%,99.1%] (309/316)	95.2% [92.1%,97.3%] (295/310)	2.6% [-0.3%,5.5%]
Acute Procedural Success by QCA	94.1% [90.9%,96.4%] (301/320)	94.7% [91.6%,96.9%] (302/319)	-0.6% [-4.2%,3.0%]
Post Procedure In-Stent % DS Range (min,max)	5%±13% [-6.6%,100%] (316)	8%±12% [-30%,100%] (310)	-3.3% [-5.3%,-1.3%]
6 Months Follow-up In-Stent % DS Range (min,max)	37%±19% [-9%,80%] (101)	34%±20% [-10%,80%] (109)	3.7% [-1.6%,9.0%]
6 months Follow-up In-Stent Binary Restenosis rate	24.8% [16.7%,34.3%] (25/101)	22.9% [15.4%,32.0%] (25/109)	1.8% [-9.7%,13.4%]
TLR-free at 6 months* (K-M)	91.6% [88.2%,94.4%]	91.9% [89.0%,94.8%]	-0.3% [-4.6%,4.0%]
TVF-free at 6 months*(K-M)	85.8% [82.1%,89.5%]	87.7% [84.2%,91.2%]	-1.8% [-7.1%,3.4%]
Safety Measures and Other Clinical Events			
In-Hospital Clinical Events	6.4% [4.0%,9.6%] (21/330)	5.1% [3.0%,8.1%] (17/331)	1.2% [-2.3%,4.8%]
Out-of-Hospital Clinical Events	10.6% [7.5%,14.4%] (35/330)	9.7% [6.7%,13.4%] (32/331)	0.9% [-3.7%,5.5%]
Bleeding Complications	1.8% [0.7%,3.9%] (6/330)	1.5% [0.5%,3.5%] (5/331)	0.3% [-1.6%,2.3%]
Vascular Complications	3.6% [1.9%,6.3%] (12/330)	3.3% [1.7%,5.9%] (11/331)	0.3% [-2.5%,3.1%]
Stent Thrombosis	0.0% [0.0%,0.9%] (0/330)	0.6% [0.1%,2.2%] (2/331)	-0.6% [-1.4%,0.2%]
Survival at 30 days (K-M)	99.4% [98.0%,100%]	99.7% [99.3%,100%]	-0.3% [-1.0%,0.5%]
Survival at 180 days (K-M)	98.1% [96.7%,99.5%]	99.4% [98.6%,100%]	-1.3% [-2.9%,0.4%]
MACE rate at 6 month	16.1% [12.3%,20.5%] (53/330)	14.8% [11.2%,19.1%] (49/331)	1.3% [-4.3%,6.8%]
Hospitalization Post-Intervention (days)	1.55±2.04 {0,32} (330)	1.40±1.08 {0,11} (331)	0.1 [-0.1,0.4]

MACE: Major Adverse Cardiac Event (includes death, MI, and emergent CABG or target lesion revascularization).

TLR free: No target lesion revascularization.

TVF free: No death, any MI or target vessel revascularization.

QCA: Quantitative Coronary Angiography

% DS: Diameter Stenosis

Stent Thrombosis: Stent thrombosis was defined as total thrombotic stent occlusion documented by angiography.

- In-hospital major clinical event: death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke prior to discharge, as determined by the independent Clinical Events Committee.
- Out-of-hospital major clinical event: death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke after discharge, as determined by the independent Clinical Events Committee.
- Bleeding complications: transfusions due to blood loss resulting from the percutaneous revascularization procedure.
- Device success: Attainment of <30% in-stent residual stenosis using the randomized treatment strategy only.
- Acute procedural success: <50% stenosis in-stent (or in-lesion if no in-stent measurement available) and freedom from in-hospital major adverse cardiac events (death, MI, emergent CABG, or repeat target lesion revascularization).

*Survival estimates by Kaplan-Meier method; Standard Error estimates by Greenwood formula

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10.4.3 Stent Delivery Failures

The stent could not be implanted (i.e., failure to cross lesion or deliver intended device) in 3% (10/330) of Micro Stent® II patients and 4.8% (16/331) of Palmaz-Schatz® Stent patients. The stent was not delivered in 5 Micro Stent® II patients and 8 Palmaz-Schatz® Stent patients. These patients were subsequently treated as follows: 5 emergent CABG procedures (1 Micro Stent® II, 4 Palmaz-Schatz® Stent); 6 non-stent percutaneous procedures (PTCA/Rotablator only) (3 Micro Stent® II, 3 Palmaz-Schatz® Stent); and, two crossovers to the other stent (1 Micro Stent® II, 1 Palmaz-Schatz® Stent). Other reasons for stent failure (e.g., misplaced deployment, embolization, and balloon burst) occurred infrequently in both groups.

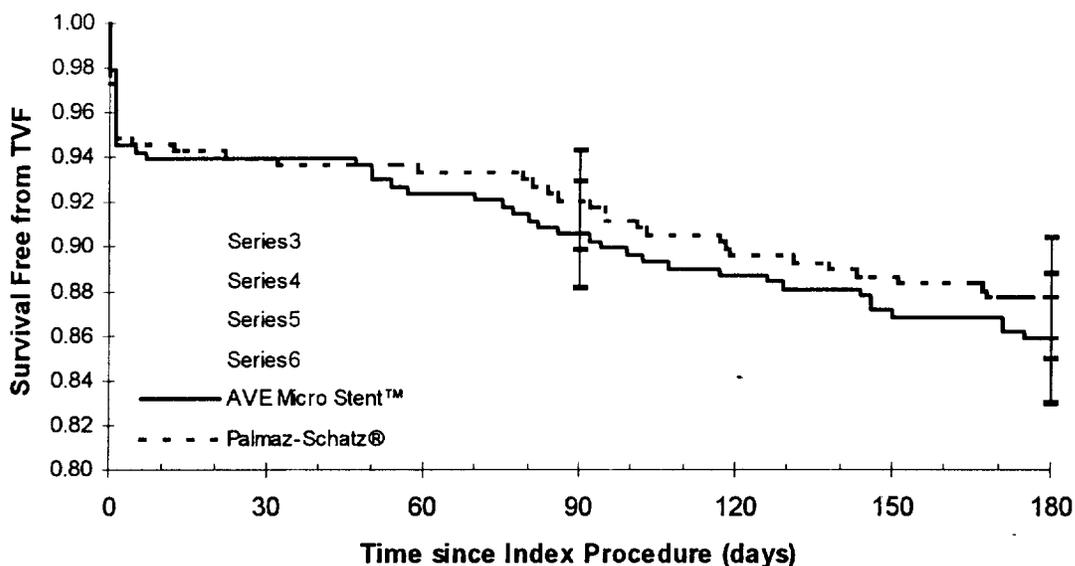
This study was performed using high-pressure balloon inflation to optimize stent deployment when necessary, and with aspirin and ticlopidine, rather than aspirin and coumadin, as the recommended anticoagulation regimen. As a consequence of these changes in stenting technique, the rates of stent thrombosis, bleeding, and vascular complications are lower than rates reported in the original Palmaz-Schatz® Stent study (Table 13). The incidence of subacute thrombosis (SAT) in the Micro Stent® II group was similar to the Palmaz-Schatz® Stent group (0.0% (0/330) vs. 0.6% (2/331), 95% CI [-1.4%, 0.2%]). One of the Palmaz-Schatz® Stent patients who had an SAT had a cardiac arrest and died during the day following the procedure. The other patient with a thrombosis had a nonfatal myocardial infarction. There were no differences in the rates of bleeding (1.8% Micro Stent® II vs. 1.5% Palmaz-Schatz® Stent) or vascular complications (3.6% Micro Stent® II vs. 3.3% Palmaz-Schatz® Stent) between the two groups.

The data on use of post-stent high-pressure balloon inflations to optimize stent deployment was examined in detail. As expected, the majority of stented lesions required a final high-pressure balloon inflation to optimize stent deployment. The majority of these high-pressure inflations were in the 16 - 18 atmosphere range, and there were no significant differences in the distribution of inflation pressures between the two groups.

10.4.4 Long Term Results

Six month follow-up was available on 302 of 330 Micro Stent® II patients (92%) and 295 of 331 (89%) of Palmaz-Schatz® Stent patients. Comparison of six-month endpoints showed no difference between the two groups. The clinical Target Vessel Failure (TVF) rate (composite of death, nonfatal myocardial infarction, need for repeat target vessel revascularization (TVR) by CABG or PTCA at six months) as calculated by Kaplan Meier method was 14.2% for the Micro Stent® II and 12.3% for the Palmaz-Schatz® Stent (95% C.I. [-7.1%, 3.4%]). Individual analysis of event rates for death, nonfatal myocardial infarction, CABG, re-PTCA, TVR, TLR, and in- or out-of-hospital results indicated no difference between the two groups (Table 13). Six-month survival curves for TVF were also constructed (Figure 1). The two curves were similar by Log-Rank and Wilcoxon testing.

**Figure 1. Freedom from Target Vessel Failure
All Randomized Patients Treated (N=661)**



	Time after initial procedure (days)					
	0	7	14	30	90	180
AVE Micro Stent II™						
# At risk	323	308	308	307	293	256
# Events	7	20	20	20	31	46
Survived	97.9%	93.9%	93.9%	93.9%	90.5%	85.8%
% SE	0.8%	1.3%	1.3%	1.3%	1.6%	1.9%
Palmaz-Schatz®						
# At risk	322	310	309	307	295	256
# Events	9	18	19	20	26	40
Survived	97.3%	94.6%	94.3%	93.9%	92.1%	87.7%
% SE	0.9%	1.2%	1.3%	1.3%	1.5%	1.8%
Tests Between Groups						
	Test	Chi-Square	Deg Frdm	P-value		
	Log-Rank	0.27	1	0.60		
	Wilcoxon	0.29	1	0.59		

The equivalence of the major endpoints, Target Lesion and Target Vessel Failure, were largely driven by the rates of revascularization. This finding was expected. Substantial bias in the determination of which patients were appropriate for revascularization (due to the nonblinded nature of this study) could significantly impact on interpretation of overall results. The clinical signs and symptoms for the 12% of patients who underwent TLR and the 12.4% of patients who underwent TVR were reviewed. Recurrent angina was the reason for a repeat procedure in 71% (29/41) of Micro Stent® II patients and 71% (27/38) of Palmaz-Schatz® Stent patients who underwent TLR. Emergent TLR was performed in 5% (2/41) of Micro Stent® II patients and 13% (5/38) of Palmaz-Schatz® Stent patients. Rates for revascularization on the basis of a positive functional study or an angiographic stenosis of $\geq 70\%$ were also equivalent between the two groups. Results from blinded adjudication of cases support the long-term equivalence of the two stents.

A subset of 291 patients qualified for angiographic restudy at six months. At the time of PMA submission the sponsor reported on 101 Micro Stent® II patients and 109 Palmaz-Schatz® Stent

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patients. (A 200 patient group would be expected to detect a difference of 0.2 mm with roughly 80% power. A 0.2-mm difference has been demonstrated in prior coronary studies to correlate with clinically significant differences between groups.) The six-month data showed no significant differences between the two groups. The six month angiographic in-stent restenosis rate for the Micro Stent® II was 24.8% compared to 22.9% for the Palmaz-Schatz® Stent (95% CI [-9.7%, 13.4%]). The mean per cent diameter stenosis was 37% versus 34% and the minimal lumen diameter was 1.86 versus 2.00 mm for the Micro Stent® II and Palmaz-Schatz® Stent, respectively.

10.4.5 Deaths

There were 9 patient deaths. Seven (2.1%) occurred in the Micro Stent® II group and 2 (0.6%) occurred in the Palmaz-Schatz® Stent group (95% C.I. [-0.2%, 3.3%]). There were 2 acute deaths in the Micro Stent® II group and one acute death in the Palmaz-Schatz® Stent group. The early death in the Palmaz-Schatz® Stent group resulted from a stent thrombosis within 12 hours of placement of the stent. One of the 5 late Micro Stent® II deaths was due to a non-cardiac cause (pneumonia and metastatic pheochromocytoma), and another death occurred after a CABG procedure. Each death was summarized in the Clinical Report and additional information was enclosed in the PMA. Review of this information did not reveal any unexpected findings.

10.4.6 Myocardial Infarctions

A total of 5 patients had a Q-wave MI: 2 (0.6%) for the Palmaz-Schatz® Stent group and 3 (0.9%) for the Micro Stent® II group. A total of 30 patients had non-Q-wave MI: 13 (3.9%) in the Palmaz-Schatz® Stent group and 17 (5.2%) in the Micro Stent® II group. Each myocardial infarction was summarized in the Clinical Report and additional information was enclosed in the PMA. Review of this information did not reveal any unexpected findings.

10.4.7 Revascularization Procedures

A total of 30 patients underwent CABG: 12 (3.6%) in the Palmaz-Schatz® Stent group and 18 (5.4%) in the Micro Stent® II group. Six of the CABG procedures (Micro Stent® II =2, Palmaz-Schatz® Stent =4) were performed emergently and 1 Micro Stent® II case was performed for TVR rather than the TLR indication. A total of 53 patients underwent repeat PTCA: 29 (8.8%) in the Palmaz-Schatz® Stent group and 24 (7.3%) in the Micro Stent® II group. Three of the PTCA procedures (Micro Stent® II =2, Palmaz-Schatz® Stent =1) were performed for TVR rather than TLR indications. The cumulative revascularization rates over time were also similar between the two groups. Each CABG and repeat PTCA was summarized in the Clinical Report and additional information was enclosed in the PMA. Review of this information did not reveal any unexpected findings.

10.4.8 Statistical modeling

Univariate and stepwise logistic regression modeling of clinical restenosis was performed. Stepwise logistic regression modeling indicated that post-procedure minimal lumen diameter (MLD) was the only significant independent predictor of TVF. This conclusion is consistent with modeling that has been performed for several other interventional cardiology studies.

10.5 GFX™ Stent Study

As a result of the initial European experience with the Micro Stent® II design, the basic building block of the stent was modified. The second generation GFX™ Stent is based on a 2-mm rather than 3 mm stent element. Additionally, a flat wire design was incorporated. These changes were introduced to further improve trackability, lower profile, and increase stent to vessel surface area

coverage. GFX™ Stent lengths range from 8 mm to 30 mm so that the physician can choose the length of the stent based on the length of the lesion to be treated.

10.5.1 Study Design

Short-term data were collected in order to detect untoward safety problems associated with the GFX™ Stent modifications. A 10-year experience with stenting suggests that faulty design and/or operator technique usually manifest with an increased MACE rate (composite incidence of death, nonfatal myocardial infarction, emergent CABG, or TLR) within the first 30 days. A 200 patient study was developed to compare 30-day safety and effectiveness outcomes of the GFX™ Stent with the Palmaz-Schatz® Stent arm of the SMART study. In addition the sponsor agreed to obtain 6 month angiographic follow-up on the first 125 patients enrolled in this study and to obtain 6 month clinical follow-up on the entire population.

This study was planned while the SMART Study was still ongoing. The Palmaz-Schatz® Stent arm of the SMART Study was used as a point of reference. The null hypothesis was that GFX™ Stent had a 30-day incidence of MACE > 1.5 times that observed for the Palmaz-Schatz® Stent arm of the SMART Study. Rejection of the null hypothesis would, therefore, imply that the 30-day incidence of MACE was < 1.5 times the 30-day incidence of MACE for the Palmaz-Schatz® Stent. The 200 patient sample size was agreed upon after reviewing a matrix of likely estimates for the 30 day MACE rate of the Palmaz-Schatz® Stent.

10.5.2 Patient Demographics

The GFX™ Stent study was initiated right after conclusion of the SMART Study. Inclusion/Exclusion criteria were identical to the eligibility criteria of the SMART Study. The 210 patients enrolled in the GFX™ Stent study ranged in age from 40 to 87 years (mean ± SD = 65 ± 10) and 69% of patients were male (Table 14). The target lesions were *de novo* in 90% and restenotic in 10%. Baseline demographics were compared to the 331 Palmaz-Schatz® Stent patients from the randomized study. This comparison suggested that the two patient populations were similar in composition.

Table 14. Patient Demographics - GFX™ Stent Study

	GFX™ Stent	Palmaz-Schatz® Stent	95% CI of Difference
Number Treated	210	331	
Per cent receiving assigned stent	99.2%	95.2%	Calculate
% Male	69%	70%	-9.3, 6.6%
% Diabetic	22%	17%	-2.1, 11.8%
Hypertension	61%	58%	-5.4, 11.6%
Hyperlipidemia	35%	31%	-4.3, 12.3%
Age (yr.)	65 ± 10	64 ± 11	-1.1, 2.6
Reference vessel diameter (mm)	3.03 ± 0.56 (164)	2.93 ± 0.47 (320)	0.00, 0.19
% DS pre procedure	64 ± 14% (164)	64 ± 13% (320)	-2.3, 2.7%
MLD (mm) pre procedure	1.10 ± 0.50 (164)	1.06 ± 0.39 (320)	-0.04, 0.12

10.5.3 Acute Procedural Results

Acute quantitative coronary angiography (QCA) analysis was completed on 78% (164/210) of the study patients at the time of PMA submission. Lesion length was statistically larger in the GFX™ Stent study (13.7 ± 6.6 mm vs. 12.1 ± 6.2 mm, 95% CI [0.3, 2.7]). The difference noted, however, is not clinically significant. Pre-procedure minimal lumen diameter, per cent diameter

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stenosis, and reference vessel diameter were similar. Acute gain post-stent placement was slightly higher in the GFX™ Stent arm (1.82 + 0.49 vs. 1.71 + 0.56, 95% CI [0.01, 0.22]). This led to the expected decrease in post-procedure in-stent per cent diameter stenosis and increase in post-procedure in-stent minimal lumen diameter when GFX™ Stent and Palmaz-Schatz® Stent results were compared (Table 15).

The acute procedure success rate of 97.0% was similar to the 94.7% rate reported for the Palmaz-Schatz® Stent group in the randomized study (95% CI [-1.3, 5.9%]). Lesion success and device success rates were also similar. In the GFX™ Stent Study there was a 1.0% (2/210) incidence of stent thrombosis, a 0.0% incidence of 30 day bleeding complications, and a 0.5% incidence of 30 day vascular complications. The bleeding and vascular complication rates were lower than the Palmaz-Schatz® Stent control while the stent thrombosis rate was similar to the Palmaz-Schatz® Stent result.

**Table 15. Principal Effectiveness and Safety Results
GFX™ Stent Study (N=210) vs. Palmaz-Schatz® Stent (N=331)**

Efficacy Measures	AVE GFX Stent™ (N=210)	Palmaz-Schatz® (N=331)	Relative Risk [95% C.I.]	Difference [95% C.I.]
Device Success (by QCA)	98.8% (162/164)	95.2% (295/310)	1.04 [1.00,1.08]	3.6% [0.7%,6.5%]
Acute Procedural Success (by QCA)	97.0% (159/164)	94.7% (302/319)	1.02 [0.98,1.07]	2.3% [-1.3%,5.9%]
Post Procedure In-Stent MLD (mm) Range (min,max)	2.92±0.44 (164) (1.68,3.95)	2.77±0.46 (310) (0.00,5.03)	N/A	0.15 [0.06,0.24]
Post Procedure In-Stent % DS Range (min,max)	4%±12% (164) (-30%,38%)	8%±12% (310) (-30%,100%)	N/A	-3.6% [-5.9%,-1.3%]
Safety Measures and Other Clinical Events				
In-Hospital MACE	3.3% (7/210)	5.1% (17/331)	0.65 [0.28,1.53]	-1.8% [-5.2%,1.6%]
In-Hospital Clinical Events	3.3% (7/210)	5.1% (17/331)	0.65 [0.28,1.53]	-1.8% [-5.2%,1.6%]
Out-of Hospital MACE (30 days)	0.5% (1/210)	0.9% (3/331)	0.53 [0.06,4.83]	-0.4% [-1.8%,1.0%]
Out-of-Hospital Clinical Events (30 days)	0.5% (1/210)	0.9% (3/331)	0.53 [0.06,4.83]	-0.4% [-1.8%,1.0%]
Bleeding Complications (30 days)	0.0% (0/210)	1.5% (5/331)	0.00 [0.00,0.00]	-1.5% [-2.8%,-0.2%]
Stroke (30 days)	0.0% (0/210)	0.0% (0/331)	- [-,-]	0.0% [-,-]
Vascular Complications (30 days)	0.5% (1/210)	3.0% (10/331)	0.16 [0.03,0.93]	-2.5% [-4.6%,-0.5%]
Stent Thrombosis	1.0% (2/210)	0.6% (2/331)	1.58 [0.23,10.94]	0.3% [-1.2%,1.9%]

Numbers are % (counts/sample size). CI = Confidence Interval.

Relative risk = AVE GFX™/Palmaz-Schatz® SE = $\sqrt{\{(1-p_1)/n_{11} + (1-p_2)/n_{21}\}}$ CI = $RR \cdot \exp(\pm 1.96 \cdot SE)$

Difference = AVE GFX™/Palmaz-Schatz® SE = $\sqrt{\{p_1 \cdot q_1/n_{11} + p_2 \cdot q_2/n_{21}\}}$ CI = $Diff \pm 1.96 \cdot SE$

- **Device success:** Attainment of <30% in-stent residual stenosis using the assigned treatment strategy only.
- **Acute procedural success:** <50% stenosis in-stent (or in-lesion if no in-stent measurement available) and freedom from in-hospital major adverse cardiac events (death, MI, emergent CABG or repeat target lesion revascularization).
- **In-hospital major clinical event:** death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke, prior to discharge as determined by the independent Clinical Events Committee.
- **Out of hospital major clinical event:** 30 day death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke after discharge, as determined by the independent Clinical Events Committee.
- **Bleeding complications:** transfusions due to blood loss resulting from the percutaneous revascularization procedure.

10.5.4 Stent Delivery Failures

The assigned stent could not be implanted (i.e. failure to cross lesion or deliver intended device) in 1.7% (4/233 stents) of attempts. In two cases, switching to a combination of shorter length stents (8 and 18 mm lengths) from the initially chosen 30-mm length allowed for successful coverage of the intended lesion. (Stents become less flexible as their length increases so that switching to shorter lengths in cases where tortuous anatomy prevents long stent placement is a standard technique.) Review of other reasons for stent delivery failure (e.g., misplaced deployment, and embolization) indicated that stent delivery failure occurred infrequently. All stent delivery failure cases were individually summarized in the PMA. Review of this information did not produce any unexpected information.

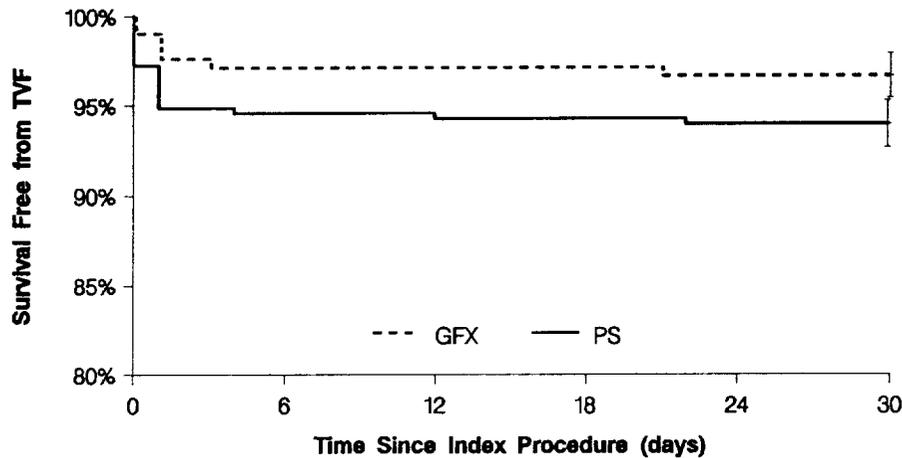
10.5.5 Short-Term Results

Thirty-day follow-up was available on 205 of 210 GFX™ Stent Study patients (98%) and 307 of 331 (93%) of Palmaz-Schatz® Stent patients. Comparison of 30-day endpoints showed no difference between the two groups. The clinical TVF rate (composite of death, nonfatal myocardial infarction, need for repeat TVR by CABG or PTCA at 30-days) as calculated by Kaplan Meier method was 3.4% for the GFX™ Stent and 6.1% for the Palmaz-Schatz® Stent. Individual analysis of event rates for death, nonfatal myocardial infarction, CABG, re-PTCA, TVR, TLR, and in- or out-of-hospital results indicated no difference between the two groups (Table 15). Thirty-day survival curves for TVF were also constructed (Figure 2). The two curves were similar by Log-Rank and Wilcoxon testing.

Figure 2. Freedom from Target Vessel Failure

AVE GFX™ Stent Study vs. Palmaz-Schatz® stent (n=541)*

* N=541 combines all patients from the GFX™ Stent Study (n=210) and all patients from the Palmaz-Schatz® arm of the SMART RCT (n=331)



	Time after initial procedure (days)			
	0	7	14	30
AVE GFX Stent™				
# At risk	208	202	200	110
# Events	2	6	6	7
% Survived	99.0%	97.1%	97.1%	96.6%
% SEM	0.6%	1.2%	1.2%	1.2%
Palmaz-Schatz®				
# At risk	322	310	309	307
# Events	9	18	19	20
% Survived	97.3%	94.6%	94.3%	93.9%
% SEM	0.9%	1.2%	1.3%	1.3%
Tests Between Groups				
	Test	Chi-Square	Deg Frdm	P-value
	Log-Rank	2.90	1	0.09
	Wilcoxon	3.06	1	0.08

10.5.6 Deaths, Myocardial Infarctions and Repeat PTCA

There was 1 death, no Q-wave myocardial infarctions, 6 non-Q-wave myocardial infarctions, no CABG procedures, and 1 re-PTCA procedures. Each major complication was summarized in the

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Clinical Report and additional information was provided in the PMA. Review of this information did not reveal any unexpected problems.

At the time of PMA Amendment submission, 30 day clinical follow-up had been obtained on 98% (205/210) of the patients enrolled in the study. The 30 day MACE rate was similar to the Palmaz-Schatz® Stent result reported in the SMART Study (GFX™ Stent was 3.8% (8/210) and the Palmaz-Schatz® Stent was 6.0% (20/331) (95% CI Difference [-5.9, 1.4%]). These values resulted in rejection of the null hypothesis and acceptance of the alternative hypothesis (30-day MACE rate < 1.5 times the Palmaz-Schatz® Stent rate). No differences were seen when individual rates for death, total non-fatal myocardial infarction, Q-wave myocardial infarction, non-Q-wave myocardial infarction, TLR, or TVR were compared.

10.6 Restenotic Lesions

Restenotic lesions were included in this study because literature data suggests that the chronic target lesion failure rate for stented restenotic lesions is very similar to the chronic rate for stented *de novo* lesions when important covariates such as diabetes mellitus and lesion size are properly taken into account. One would expect a chronic TVF rate of less than 1.3 times that of *de novo* lesions for stented restenotic lesions. (The comparable balloon angioplasty rate for retreatment of a restenotic lesion would be expected to be at least 30% higher than the stent rate.)

Enrollment of restenotic lesions into the randomized study was limited. Twenty-one restenotic lesions (6%) were treated in the Micro Stent® II group and 10 (3.0%) lesions were treated in the Palmaz-Schatz® Stent group. In addition, 45 of the 160 lesions (28%) treated with 39-mm stent in the long lesion study were restenotic lesions. Review of the baseline and acute post-procedural information for the *de novo* and restenotic lesions enrolled in the randomized and long lesion studies did not suggest any striking differences between the groups. The small patient numbers limits a more formal comparison.

Acute and chronic success rates for the randomized study restenotic lesion groups have been separately analyzed. An acute procedure success rate of 95.2% and a 6 month TLR-free rate of 95.2% was noted for the 21 Micro Stent® II lesions. The corresponding values for the 45 lesions studied in the 39-mm stent study were 88% and 84%. These acute and chronic results for the Micro Stent® II restenotic lesion subset compares favorably with corresponding *de novo* Micro Stent® II and Palmaz-Schatz® Stent results. In addition, multivariate statistical modeling performed for both the randomized and long lesion studies did not indicate that prior restenosis was a risk factor for chronic target vessel failure.

In conclusion, small patient numbers currently limits analysis of stented restenotic lesions. Analysis of available data, however, did not produce any unexpected findings. Step-wise logistic regression modeling indicated that *de novo* vs. restenotic lesion type was not a significant predictor of TVF at six months. These results were expected. Prior literature has suggested that when important baseline and procedural covariates are similar (e.g. incidence of diabetes, post-procedure per cent diameter stenosis etc.), there is not a big difference between results for *de novo* and restenotic lesions.

11. CONCLUSIONS DRAWN FROM THE STUDIES

11.1 Safety

The preclinical studies conducted on the Micro Stent® II and GFX™ Stent 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 material 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 both stents and their delivery system met product specifications and that they are safe for clinical use.

The results of *in vivo* animal testing that was conducted on the Micro Stent® II and GFX™ Stent demonstrated that acute and chronic *in vivo* performance characteristics and sterility are safe for clinical use.

11.2 Effectiveness

The results of the clinical studies indicate that the objectives of each study were met, the MACE rates between groups are comparable, the TVF rates are low, and that the data support the indications for use of the Micro Stent® II and GFX™ Stent.

Data from the randomized SMART study indicate that the Micro Stent® II performs both acutely and chronically at least as well as the Palmaz-Schatz® Stent. The acute, 30-day, and six month clinical and angiographic point estimates obtained for major clinical variables support the safety and effectiveness Micro Stent® II and GFX™ Stent.

Data provided in this PMA support a broader indication for coronary stenting. The original Palmaz-Schatz® Stent studies focused on a narrow group of patients with short (≤ 15 mm), *de novo* lesions in the proximal to midportion of native coronary arteries. Results generated in both the randomized SMART study and long lesion study support approval of primary stenting for treatment of longer lesions (≤ 30 mm).

The data presented on the GFX™ Stent are sufficient for approval purposes when considered in the full context of prior engineering and clinical developmental work that has been performed by the sponsor. Two limitations were considered in interpretation of this data set: the sponsor chose to compare these data to a nonrandomized control, and, there are no supporting six month angiographic or clinical data for the current study.

On the other hand, the engineering modifications incorporated in the GFX™ Stent design have been well thought out and executed. These modifications were implemented based on initial feedback from Micro Stent® II users and represent minor modifications of the original Micro Stent® II design concept. In every major category, the GFX™ Stent appears to be at least equivalent to the Palmaz-Schatz® Stent. Therefore, approval of the GFX™ Stent based on the above data is reasonable because:

- 1) the Micro Stent® II results from the randomized study are acceptable and
- 2) the GFX™ Stent is a minor modification of the original Micro Stent® II design.

In addition, The sponsor has committed to extensive 6-month angiographic and clinical follow-up on the GFX™ Stent patients. As part of routine post-market surveillance, clinical follow-up every year for five years will be implemented for these patients.

11.3 Complication Rates

The high bleeding and vascular complication rates associated with stenting that were reported in the original Palmaz-Schatz® Stent studies were mainly due to the aggressive anticoagulation regimen employed after stenting to reduce the rate of subacute thrombosis. There has been a major shift during the last two years to the use of aspirin/ticlopidine rather than aspirin/coumadin. The risk/benefit ratio associated with stenting has been favorably altered as a result of changes in drug therapy. In this PMA, the subacute thrombosis rate was low, and bleeding and vascular

complication rates were substantially reduced in comparison to the early stent experience.

The rate of device deployment complications was acceptable when compared to the Palmaz-Schatz® Stent.

11.4 Labeling

To provide additional insight in selecting and treating patients with a coronary artery stent, labeling for these devices will contain the following statements:

- The risks and benefits described above should be carefully considered for each patient before use of the Micro Stent® II / GFX™ Stent Over-the-wire Stent System. Patient selection factors to be assessed should include a judgment regarding risk of prolonged anticoagulation. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease). (See Contraindications)
- Premorbid conditions that increase the risk of a poor initial result or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure and severe obesity) should be reviewed. **For the Micro Stent® II** - The two statistically significant predictors of Clinical Restenosis (Target Vessel Revascularization) for the Micro Stent® II were post-procedural Minimum Lumen Diameter (MLD) and Reference Vessel Diameter (RVD). Clinical Restenosis was less likely with larger MLDs and RVDs.
- Thrombosis following stent implantation is affected by several baseline angiographic and procedural factors. These include vessel diameter less than 3.0 mm, vessel thrombosis, poor distal flow and/or dissection following stent implantation. In patients that have undergone coronary stenting, the persistence of a thrombus or dissection is considered a marker for subsequent thrombotic occlusion. These patients should be monitored very carefully during the first month after stent implantation.
- The safety and effectiveness of the Micro Stent® II / GFX™ Stent have not been established in the following patient populations:
 - Patients with **unresolved vessel thrombus at the lesion site**.
 - Patients with coronary artery **reference vessel diameter < 3 mm**.
 - Patients with **lesions located** in the left main coronary artery, ostial lesions or lesions located at a bifurcation.
 - Patients with diffuse disease or **poor outflow distal** to the identified lesions.
 - Patients with a recent **acute myocardial infarction** where there is evidence of thrombus or poor flow.
 - Patients with **more than two overlapping stents** due to risk of thrombus or poor flow.
 - Patients for longer than 6 months follow-up for the Micro Stent® II / 30 days follow-up for the GFX™ Stent.
- The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters to treat in-stent stenosis has not been established.

11.5 Post-Approval Studies

Although enough information has been presented for approval purposes, there is much that can be gained from continued analysis of the sponsor's data. Conditions of approval indicate that complete follow-up of the randomized patient group be obtained at six months, one year, and then

yearly thereafter for a total of five years, and that the sponsor make a concerted effort to obtain autopsies on patients who die.

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

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

The FDA issued an approval order to Arterial Vascular Engineering on December 23, 1997. The approval order stipulated that in addition to the standard postapproval requirements, the postapproval reports must include the following information: (1) further characterization of long-term safety and effectiveness by following for 5 years from implant at least 250 of the 330 patients implanted with the Micro Stent® II; and at least 160 of the 210 patients implanted with the GFX™ Stent in the SMART trial; (2) the protocol for this study and study timelines will be submitted to the agency for review within 30 days of approval, and the final protocol will be developed interactively with the FDA review team; and, (3) summary reports will be submitted to the agency annually and a final report at the end of the study. FDA inspection of Arterial Vascular Engineering's manufacturing facility determined it was in compliance with the Device Good Manufacturing Practices Regulation (21 CFR part 820).

14. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to health from use of the device: See indications, contraindications, warnings, precautions and adverse events in the labeling.

Postapproval requirements and restrictions: See approval order.

The Approval Order, Summary of Safety and Effectiveness Data, and labeling can be found on the Internet at address <http://www.fda.gov/cdrh/pmapage.html>.

AVE MICRO STENT® II OVER-THE-WIRE CORONARY STENT SYSTEM

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1. DEVICE DESCRIPTION

The AVE Micro Stent® II Over-the-wire Coronary Stent System includes:

- A pre-mounted 316L stainless steel stent.
- A sheathless, over-the-wire Over-the-wire Coronary Stent System providing uniform, symmetrical stent deployment.
- Two radiopaque (gold) markers imbedded in the inner shaft beneath the balloon, proximal and distal to the stent. The markers are as visualized under fluoroscopy.
- A third and fourth shaft marker is located at 95cm and 105cm, respectively from the distal tip.

Figure 1- AVE Micro Stent® II graphic

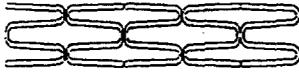


Table 1. Device Specifications

Stent Diameter	Stent Lengths	Minimum Guiding Catheter Inner Diameter*	Stent Deployment Pressure	Rated Burst Pressure	Stent Free % Area
3.0 mm	6, 9, 12, 15, 18, 24 mm	0.072 inch	9 atm	9 atm	83
3.0 mm	30 mm	0.076 inch	9 atm	9 atm	83
3.5 mm	6, 9, 12, 15, 18, 24 mm	0.072 inch	9 atm	9 atm	85
3.5 mm	30 mm	0.076 inch	9 atm	9 atm	85
4.0 mm	6, 9, 12, 15, 18, 24, 30 mm	0.076 inch	9 atm	9 atm	87

* See individual manufacture specifications for (Fr.) equivalent.

2. INDICATIONS

The AVE Micro Stent® II Over-the-wire Coronary Stent System is indicated for use in patients eligible for balloon angioplasty with symptomatic ischemic disease due to discrete *de novo* lesions in native coronary arteries (length \leq 30 mm) with a reference vessel diameter of 3.0 mm to 4.0 mm. Stenting is intended to improve coronary luminal diameter (See Individualization of Treatment). Long term outcome (beyond 6 months) for this permanent implant is unknown at present.

3. CONTRAINDICATIONS

The AVE Micro Stent® II Over-the-wire Coronary Stent System is contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.
- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon.

4. WARNINGS

- Since the use of this device carries the associated risk of subacute thrombosis, vascular complications and / or bleeding events, judicious selection of patients is necessary.
- Patients allergic to 316L stainless steel may suffer an allergic reaction to this implant.

5. PRECAUTIONS

(See also Individualization of Treatment)

- Only physicians who have received appropriate angioplasty training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent restenosis may require re-dilatation of the arterial segment containing the stent. The long-term outcome following repeat dilatation of coronary stents is unknown.
- When multiple stents are required, stent materials should be of similar composition.

5.1 Stent Handling – Precautions

- **For single use only.** Do not resterilize or reuse. Note product "Use Before" date.
- The AVE Micro Stent® II Over-the-wire Coronary Stent System is designed **not** to be removed from its delivery balloon. The AVE Micro Stent® II is not designed to be crimped onto another balloon. Removing the stent from its delivery balloon may damage the stent and/or lead to stent embolization.
- Special care must be taken not to handle or in any way disrupt the stent position on the delivery device. This is most important during catheter removal from packaging, placement over guide wire and advancement through hemostasis valve adapter and guiding catheter hub.
- Excessive manipulation, e.g. rolling the mounted stent may cause dislodgment of the stent from the delivery balloon
- Use only the appropriate balloon inflation media. Do not use air or any gas medium to inflate the balloon as it may cause uneven expansion and difficulty in deployment of the stent.

5.2 Stent Placement – Precautions

- Do not prepare or pre-inflate the balloon prior to stent deployment, other than as directed. Use balloon purging technique described in the Instruction for Use.

- Implanting a stent may lead to dissection of the vessel distal and / or proximal to the stent and may cause acute closure of the vessel requiring additional intervention (e .g. CABG, further dilatation, placement of additional stents, or other).
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the proximal lesion. Stenting in this order obviates the need to cross the proximal stent when placing the distal stent and reduces the chances for dislodging the proximal stent.
- Do not expand the stent if it is not properly positioned in the vessel. (See Stent/System Removal- Precautions)
- Placement of the stent has the potential to compromise side branch patency.
- Balloon pressures should be monitored during inflation. **Do not exceed rated burst pressure as indicated on product label.** (See Balloon Inflated Diameter dimensions in Table 5). Use of pressures higher than specified on product label may possibly result in a ruptured balloon and potential intimal damage and dissection.
- **Do not attempt to pull an unexpanded stent back through the guiding catheter, dislodgment of the stent from the balloon may occur.** (See Stent/System Removal-Precautions)
- Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the vascular access site. Complications may include bleeding, hematoma or pseudoaneurysm.

5.3 Stent / System Removal- Precautions

Should unusual resistance be felt at any time, either during lesion access or during removal of the Stent Delivery System post-stent implantation, the Stent Delivery System and guiding catheter should be removed as a single unit. This must be done under direct visualization of fluoroscopy.

When removing the Delivery System as a single unit:

- It's recommended to maintain guidewire placement across the lesion and carefully pullback the Stent Delivery System until the proximal balloon marker of the Stent Delivery System is aligned with the distal tip of the guiding catheter. **Do not pull the Stent Delivery System into the guiding catheter.**
- The guiding catheter and Stent Delivery System should be carefully removed from the coronary artery as a single unit.
- The system should be pulled back into the descending aorta toward the arterial sheath.
- As the distal end of the guiding catheter enters into the arterial sheath, the catheter will straighten allowing safe withdrawal of the Stent Delivery System into the guiding catheter and the subsequent removal of the stent delivery system from the arterial sheath.

- Failure to follow these steps and / or applying excessive force to the Stent Delivery System can potentially result in loss or damage to the stent or Stent Delivery System components such as the balloon.

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

5.4 Post-Stent Placement – Precautions

- Care must be exercised when crossing a newly deployed stent an intravascular ultrasound (IVUS), or a coronary guidewire, or balloon catheter, to avoid disrupting the stent geometry.
- Do not perform Magnetic Resonance Imaging (MRI) scan on patients post-stent implantation until the stent has been completely endothelialized (eight weeks) to minimize the potential for migration. The stent may cause artifacts in MRI scans due to distortion of the magnetic field.

6. ADVERSE EVENTS

A total of 874 patients were enrolled in two multi-center clinical trials to evaluate the safety and efficacy of the balloon expandable, over-the-wire AVE Micro Stent® II Stent for treatment of symptomatic coronary artery disease. Of these 543 received to the AVE Micro Stent® II and 331 received the JJIS Palmaz-Schatz® Stent participating in the randomized SMART RCT Clinical Trial. Those patients form the basis of the observed events reported. (See Clinical Studies)

Summary of Clinical Trial Patient Enrollment (n=874)

	AVE Micro Stent® II	Control Stent	Patient Totals
Feasibility Study	213	NA	213
Randomized Trial	330	331	661
Patient Totals	543	331	874

6.1 Observed Adverse Events

A total of 119 of 543 patients (21.3%) receiving the AVE Micro stent II experienced one or more adverse events during the first 6 months of follow-up compared to 59 of 331 control patients (17.7%).

Table 2. Adverse Events During The First 6 Months
% [+95 % Confidence Interval] Number/Denominator
(n=874)

SMART TRIAL		
	AVE Micro Stent® II (n=543)	Palmaz-Schatz® (n=331)
Death Total	1.7% [0.8%,3.1%] (9/543)	0.6% [0.1%,2.2%] (2/331)
Early (in-hospital)	0.6% [0.1%,1.6%] (3/543)	0.3% [0.0%,1.7%] (1/331)
Out-of -hospital	1.1% [0.4%,2.4%] (6/543)	0.3% [0.0%,1.7%] (1/331)
Q-wave MI Total	0.7% [0.2%,1.9%] (4/543)	0.6% [0.1%,2.2%] (2/331)
Early (in-hospital)	0.6% [0.1%,1.6%] (3/543)	0.6% [0.1%,2.2%] (2/331)
Out-of -hospital	0.2% [0.0%,1.0%] (1/543)	0.0% [0.0%,0.9%] (0/331)
Non-Q-wave Total	4.6.% [3.0%,6.7%] (25/543)	3.9% [2.1%,6.6%] (13/331)
Early (in-hospital)	3.9% [2.4%,5.9%] (21/543)	3.3% [1.7%,5.9%] (11/331)
Out-of -hospital	0.7% [0.2%,1.9%] (4/543)	0.6% [0.1%,2.2%] (2/331)
CABG Total	3.9% [2.4%,5.9%] (21/543)	2.4% [1.0%,4.7%] (8/331)
Early (in-hospital)	1.3% [0.5%,2.6%] (7/543)	1.2% [0.3%,3.1%] (4/331)
Out-of -hospital	2.6% [1.4%,4.3%] (14/543)	1.2% [0.3%,3.1%] (4/331)
Stent Thrombosis Total	0.6% [0.1%,1.6%] (3/543)	0.6% [0.1%,2.2%] (2/331)
Early (in-hospital)	0.6% [0.1%,1.6%] (3/543)	0.3% [0.0%,1.7%] (1/331)
Out-of -hospital	0.0% [0.0%,0.6%] (0/543)	0.3% [0.0%,1.7%] (1/331)
Bleeding Requiring Transfusion-Procedural	1.8% [0.9%,3.4%] (10/543)	1.5% [0.5%,3.5%] (5/331)
Vascular Complications	5.5% [3.8%,7.8%] (30/543)	3.3% [1.7%,5.9%] (11/331)
Cerebrovascular Accidents	0.7% [0.2%,1.9%] (4/543)	0.0% [0.0%,0.9%] (0/331)
Stent Delivery Failure	2.4% [1.3%,4.1%] (13/543)	4.8% [2.8%,7.7%] (16/331)

NOTE: * In cases where a patient experienced both an in-hospital event and an out-of-hospital event they are counted once in each group.

They are counted only once in the event total. Hence, the sum of the in-hospital event rate and the out-of-hospital event rate may not equal the total event rate.

A total of nine of the 543 patients who received the AVE Micro Stent® II died during the clinical study. The three in-hospital deaths included one myocardial infarction at 192 hours after the stent placement and cardiac arrests occurring at 9 and 48 hours after stenting. The six out of hospital deaths occurred between 47 days and 244 days after stenting included myocardial infarction (n=2), cardiac arrest (n=3) and; pneumonia (n=1).

Stent thrombosis in the patients who received the AVE Micro Stent® II. The incidence of vascular complications after stent placement 5.5% (30/ 543) patients. The rate for procedural bleeding requiring transfusion was 1.8% (10/ 543) patients.

Initial delivery failure occurred in 1.8% (13/543) patients as follows: operator was unable to deliver first stent (n=7), and failure to delivered assigned stent (n=7).

6.2 Potential Adverse Events

Adverse events (in alphabetical order) may be associated with the use of a coronary stent in native coronary arteries may include:

- Acute myocardial infarction
- Arrhythmia's (including VF and VT)
- Coronary artery bypass surgery
- Death
- Dissection
- Drug reactions to antiplatelet agents/ contrast medium
- Emboli, distal(air, tissue or thrombotic emboli)
- Emergent Coronary Artery Bypass Surgery
- Hemorrhage, requiring transfusion
- Hypotension / Hypertension
- Infection and pain at insertion site.
- Ischemia, myocardial.
- Perforation.
- Pseudoaneurysm, femoral
- Restenosis of stented segment
- Spasm
- Stent embolization
- Stent thrombosis/occlusion.
- Stroke/Cerebrovascular Accidents
- Total occlusion of coronary artery

7. CLINICAL STUDY

A total of six hundred and sixty-one (661) patients were treated at forty (40) North American Investigational sites in SMART, a multicenter, randomized, prospective controlled clinical trial in order to evaluate the safety and efficacy of the AVE Micro Stent® II (n=330) as compared to the JJIS Palmaz-Schatz® (n=331) stent in treating *de novo* and restenotic lesions in the native coronary arteries. A separate non-randomized feasibility study (n=213) was conducted prior to beginning the randomized trial. The primary end-point was defined as six-month clinically driven

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need for Target Lesion Revascularization (TLR)*. A clinical events committee blinded to the treatment arm adjudicated all major clinical events and clinically driven TLR.

Eligibility was determined by the presence of angina or positive functional study (ETT). Patients were identified for elective stenting of *de novo* or restenotic lesions in native coronary arteries having vessel diameter between 3.0 mm and 4.0 mm with a lesion length of ≤ 30 mm which could be covered by an appropriate length AVE Micro Stent® II (i.e. 6, 15 or 30 mm) or a combination thereof. These patients underwent balloon angioplasty (1:1 balloon to artery ratio) after which a stent delivery system of the appropriate size was selected and deployed in the native coronary artery. Post deployment dilatation was made using a high-pressure balloon having a 1:1 balloon to artery ratio to obtain optimal stent apposition.

The anticoagulation regimen administered to 96.8% of the patients was 325 mg / day of uncoated, water-soluble aspirin for 6 months and ticlopidine 250mg twice a day for at least 30 days. At the discretion of the investigator, alternative therapy was allowed for non-optimal results which were defined as > 30 mm stent implanted, $>10\%$ residual stenosis, any residual dissection, TIMI flow grade 0-1, or the presence of thrombus.

Clinical follow-up intervals for all treated SMART RCT patients were 30 days, 45 days, 6 months and 9 months. A subset of patients underwent angiographic follow-up at 6 months. The study randomization was successful, as both treatment groups were demographically equivalent. All treated randomized patients were included in the intent-to-treat efficacy analysis.

* TLR Definition

TLR is defined as a clinically driven repeat revascularization of a target lesion that was angiographically narrowed. The definition of "clinically driven" included a positive functional ischemia study, resting ischemia ECG changes in a distribution consistent with the target vessel, or ischemic symptoms and an angiographic minimal lumen diameter stenosis $\geq 50\%$ by QCA; revascularization of a target lesion with diameter stenosis $\geq 70\%$ by QCA without either angina or a positive functional study was also considered clinically driven.

**Table 4. Principal Effectiveness and Safety Results
AVE Micro Stent® II (Randomized Control Trial) vs. Palmaz-Schatz® Stent
(N=661)**

Efficacy Measures	AVE Micro Stent II™ (N=330)	Palmaz-Schatz® (N=331)	Difference [95% C.I.]
Device Success by QCA	97.8% [95.5%,99.1%] (309/316)	95.2% [92.1%,97.3%] (295/310)	2.6% [-0.3%,5.5%]
Acute Procedural Success by QCA	94.1% [90.9%,96.4%] (301/320)	94.7% [91.6%,96.9%] (302/319)	-0.6% [-4.2%,3.0%]
Post Procedure In-Stent % DS Range (min,max)	5%±13% {-66%,100%} (316)	8%±12% {-30%,100%} (310)	-3.3% [-5.3%,-1.3%]
6 Months Follow-up In-Stent % DS Range (min,max)	37%±19% {-9%,80%} (101)	34%±20% {-10%,80%} (109)	3.7% [-1.6%,9.0%]
6 months Follow-up In-Stent Binary Restenosis rate	24.8% [16.7%,34.3%] (25/101)	22.9% [15.4%,32.0%] (25/109)	1.8% [-9.7%,13.4%]
TLR-free at 6 months*(K-M)	91.6% [88.2%,94.4%]	91.9% [89.0%,94.8%]	-0.3% [-4.6%,4.0%]
TVF-free at 6 months*(K-M)	85.8% [82.1%,89.5%]	87.7% [84.2%,91.2%]	-1.8% [-7.1%,3.4%]
Safety Measures and Other Clinical Events			
In-Hospital Clinical Events	6.4% [4.0%,9.6%] (21/330)	5.1% [3.0%,8.1%] (17/331)	1.2% [-2.3%,4.8%]
Out-of-Hospital Clinical Events	10.6% [7.5%,14.4%] (35/330)	9.7% [6.7%,13.4%] (32/331)	0.9% [-3.7%,5.5%]
Bleeding Complications	1.8% [0.7%,3.9%] (6/330)	1.5% [0.5%,3.5%] (5/331)	0.3% [-1.6%,2.3%]
Vascular Complications	3.6% [1.9%,6.3%] (12/330)	3.3% [1.7%,5.9%] (11/331)	0.3% [-2.5%,3.1%]
Stent Thrombosis	0.0% [0.0%,0.9%] (0/330)	0.6% [0.1%,2.2%] (2/331)	-0.6% [-1.4%,0.2%]
Survival at 30 days (K-M)	99.4% [98.0%,100%]	99.7% [99.3%,100%]	-0.3% [-1.0%,0.5%]
Survival at 180 days (K-M)	98.1% [96.7%,99.5%]	99.4% [98.6%,100%]	-1.3% [-2.9%,0.4%]
MACE rate at 6 month	16.1% [12.3%,20.5%] (53/330)	14.8% [11.2%,19.1%] (49/331)	1.3% [-4.3%,6.8%]
Hospitalization Post-Intervention (days)	1.55±2.04 [0,32] (330)	1.40±1.08 [0,11] (331)	0.1 [-0.1,0.4]

MACE: Major Adverse Cardiac Event (includes death, MI, and emergent CABG or target lesion revascularization).

TLR free: No target lesion revascularization.

TVF free: No death, any MI or target vessel revascularization.

QCA: Quantitative Coronary Angiography

% DS: Diameter Stenosis

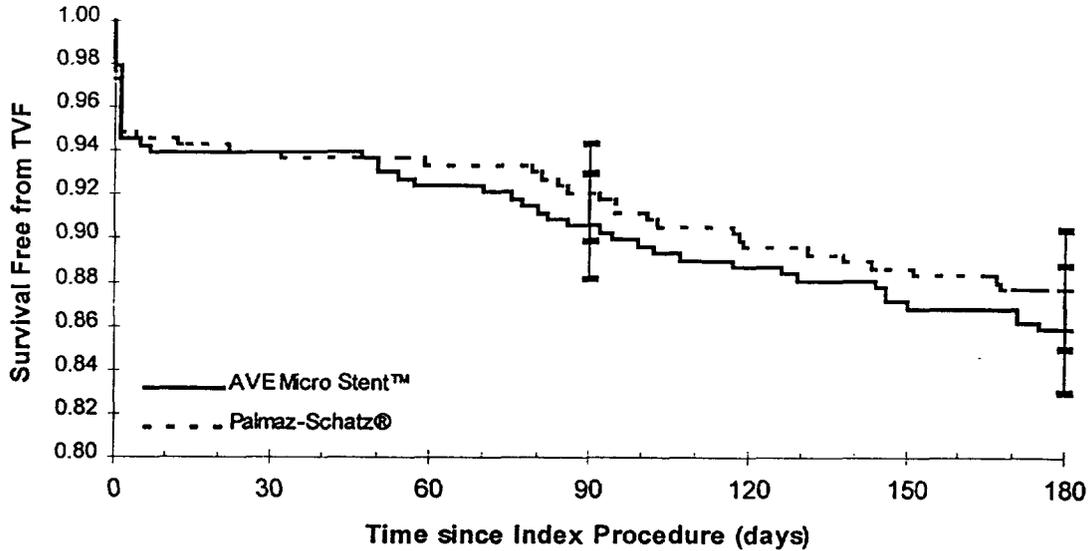
Stent Thrombosis: Stent thrombosis was defined as total thrombotic stent occlusion documented by angiography.

- In-hospital major clinical event: death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke prior to discharge, as determined by the independent Clinical Events Committee.
- Out-of-hospital major clinical event: death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke after discharge, as determined by the independent Clinical Events Committee.
- Bleeding complications: transfusions due to blood loss resulting from the percutaneous revascularization procedure.
- Device success: Attainment of <30% in-stent residual stenosis using the randomized treatment strategy only.
- Acute procedural success: <50% stenosis in-stent (or in-lesion if no in-stent measurement available) and freedom from in-hospital major adverse cardiac events (death, MI, emergent CABG, or repeat target lesion revascularization).

*Survival estimates by Kaplan-Meier method; Standard Error estimates by Greenwood formula.

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Figure 2. Freedom from Target Vessel Failure.
All Randomized Patients Treated (N=661)



	Time after initial procedure (days)					
	0	7	14	30	90	180
AVE Micro Stent II™						
# At risk	323	308	308	307	293	256
# Events	7	20	20	20	31	46
% Survived	97.9%	93.9%	93.9%	93.9%	90.5%	85.8%
% SE	0.8%	1.3%	1.3%	1.3%	1.6%	1.9%
Palmaz-Schatz®						
# At risk	322	310	309	307	295	256
# Events	9	18	19	20	26	40
% Survived	97.3%	94.6%	94.3%	93.9%	92.1%	87.7%
% SE	0.9%	1.2%	1.3%	1.3%	1.5%	1.8%
Tests Between Groups						
	Test	Chi-Square	Deg Frdm	P-value		
	Log-Rank	0.27	1	0.60		
	Wilcoxon	0.29	1	0.59		

8. INDIVIDUALIZATION OF TREATMENT

The risks and benefits described above should be carefully considered for each patient before use of the AVE Micro Stent® II Over-the-wire Coronary Stent System. Patient selection factors to be assessed should include a judgment regarding risk of prolonged anticoagulation. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g. those patients with recently active gastritis or peptic ulcer disease).

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Premorbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed. The two statistically significant predictors of Clinical Restenosis (Target Vessel Revascularization) for the **Micro Stent® II** were post-procedural Minimum Lumen Diameter (MLD) and Reference Vessel Diameter (RVD). Clinical Restenosis was less likely with larger MLDs and RVDs.

Thrombosis following stent implantation is affected by several baseline angiographic and procedural factors. These include vessel diameter less than 3 mm, vessel thrombosis, poor distal flow and or dissection following stent implantation. In patients that have undergone coronary stenting, the persistence of a thrombus or dissection is considered a marker for subsequent thrombotic occlusion. These patients should be monitored very carefully during the first month after stent implantation.

8.1 Use in Special Populations

The safety and effectiveness of the **AVE Micro Stent® II Over-the-wire Coronary Stent System** has not been established for patients with any of the following characteristics:

- Patients with **unresolved vessel thrombus at the lesion site.**
- Patients with coronary artery **reference vessel diameters < 3.0 mm.**
- Patients with **lesions located** in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation.
- Patients with **diffuse disease or poor outflow distal** to the identified lesions.
- Patients with recent **acute myocardial infarction** where there is evidence of thrombus or poor flow.
- Patients with **more than two overlapping stents** due to risk of thrombus or poor flow.
- Patients for longer than 6 months follow-up.

The safety and effectiveness of using mechanical atherectomy devices, (directional atherectomy catheters, rotational atherectomy catheters), or laser angioplasty catheters to treat in-stent stenosis has not been established.

9. HOW SUPPLIED

STERILE: This device is sterilized with e-beam radiation. It is intended for single use only. Non-pyrogenic. Do not use if package is opened or damaged.

CONTENTS: One (1) **AVE Micro Stent® II Over-the-wire Coronary Stent System.**

STORAGE: Store in a cool, dry, dark place.

10. OPERATOR'S MANUAL

10.1 Inspection Prior to Use

Carefully inspect the sterile package before opening. It is not recommended that the product be used after the "Use Before Date". If the integrity of the sterile package has been compromised prior

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to the product "Use Before Date" (e.g., damage of the package) contact your local AVE Representative for return information. Do not use if any defects are noted.

10.2 Materials Required

Quantity	Material
	Appropriate guiding catheter. (see Table 1- Device Specifications)
1	20 cc syringe
	Heparinized Normal Saline
1	0.014 inch x 300 cm guide wire
1	Rotating hemostatic valve
	Contrast medium diluted 1:1 with normal saline
1	Inflation device
1	Torque device
Optional	Three-way stopcock

10.3 Preparation

10.3.1 Guide Wire Lumen Flush

Step	Action
1	Flush Stent Delivery System guide wire lumen with heparinized saline
2	Remove protective tip covering the stent/balloon. Care should be taken not to disrupt the stent.
3	Verify that the stent is positioned between the proximal and distal balloon markers.

10.3.2 Balloon Preparation

Step	Action
1	Fill a 20 cc syringe with 5 cc of contrast/saline mixture (1:1)
2	Attach to delivery catheter and apply negative pressure for 20-30 seconds
3	Slowly release pressure to allow negative pressure to draw mixture into balloon lumen
4	Detach syringe and leave a meniscus of mixture on the hub of the balloon lumen
5	Prepare inflation device in standard manner and purge to remove all air from syringe and tubing
6	Attach inflation device to balloon directly insuring no bubbles remain at connection
7	Leave on ambient pressure (neutral position). Note: Do not pull negative pressure on inflation device after balloon preparation and prior to delivering the stent.
8	Moisten the stent with heparinized saline by submerging the stent into a sterile bowl containing the solution. Note: Do not use gauze sponges to wipe down the stent as fibers may disrupt the stent.
9	Visually inspect the stent to insure the stent is placed within the area of the proximal and distal balloon markers.
10	Check the integrity of the stent attachment on the delivery system by gently running the stent segment through the thumb and finger. If not intact, contact your AVE Representative and return the unused device to Arterial Vascular Engineering, Inc.

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10.4 Delivery Procedure

Step	Action
1	Prepare vascular access site according to standard PTCA practice.
2	Pre-dilate the lesion/vessel with appropriate diameter balloon having a ratio of 1:1 with the diameter of the vessel
3	Maintain neutral pressure on inflation device. Open rotating hemostatic valve to allow for easy passage of the stent. Note: If resistance is encountered, do not force passage . Resistance may indicate a problem and may result in damage to the stent if it is forced. Remove the system and examine.
4	Ensure guiding catheter stability before advancing the stent delivery system into the coronary artery.
5	Carefully advance the stent delivery system into the hub of the guiding catheter
6	Note: If the physician encounters resistance to the stent delivery system prior to exiting the guiding catheter, do not force passage . Resistance may indicate a problem and may result in damage to the stent if it is forced. Maintain guidewire placement across the lesion and remove the stent delivery system as a single unit. (see Removal of Unexpanded Stent Instructions).
7	Advance delivery system over the guide wire to the target lesion under direct fluoroscopic visualization. Utilize the proximal and distal radiopaque markers on the balloon as a reference point. If the position of the stent is not optimal, it should be carefully repositioned or removed (see Removal of Unexpanded Stent Instructions). Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.
8	Optimal stent placement requires the distal end of the stent to be placed approximately 1 mm beyond the distal end of the lesion.
9	Sufficiently tighten the rotating hemostatic valve. Stent is now ready to be deployed.

10.5 Deployment Procedure

Step	Action
1	Deploy stent by inflating balloon to nominal pressure to expand the stent. Note: Refer to product labeling and Table 5 for the proper inflation pressure. Do not exceed Rated Burst Pressure or expand stent beyond 4.3 mm.
2	Maintain inflation pressure for 15-30 seconds for full expansion of the stent.
3	Note: Under-expansion of the stent may result in stent movement. Care must be taken to properly size the stent to ensure the stent is in full contact with the arterial wall upon deflation of the delivery system balloon.

10.6 Removal Procedure

Step	Action
1	Deflate the balloon by pulling negative pressure on the inflation device. Allow adequate time, at least 15 seconds, for full balloon deflation. Longer stents may require more time for deflation.
2	Fully open the hemostatic valve.
3	Maintain position of guiding catheter and guidewire to prevent it from being drawn into vessel. Very slowly, withdraw the balloon from the stent maintaining negative suction, allowing movement of the myocardium to gently dislodge the balloon from stent.
4	Tighten the hemostatic valve
5	Repeat angiography and visually assess the vessel and the stent for proper expansion.
6	A second balloon inflation may be required to insure optimal stent expansion. In such instances, a non-compliant, higher-pressure balloon of adequate size (the same size as the stent delivery-system balloon or larger) and length may be used to accomplish this. NOTE: In smaller or diffusely diseased vessels, the use of high balloon inflation pressures may over-expand the vessel distal to the stent and could result in vessel dissection.
7	The final internal stent diameter should be equal to or slightly larger than the proximal and distal reference vessel diameters.
8	Repeat angiography to evaluate and determine procedure status or termination. NOTE: Should the need arise for placement of a second stent to adequately cover the lesion length, placement of the stent most distal in the artery should be done prior to placement of the proximal stent, if possible.
9	NOTE: Observation of the patient and angiographic evaluation of the stent site should be performed periodically within the first 30 minutes after stent placement. If stent placement is associated with the onset of thrombus or suspected thrombus in the region of the stented segment, intracoronary infusions of a thrombolytic agent is recommended

10.7 *in vitro* Information

**Table 5: Stent Diameter (mm) at Deployment Pressure (ATM)
Compliance Chart**

AVE Micro Stent® II Over-the-wire Coronary Stent System Stent Diameter (mm) at Deployment Pressure (ATM) Compliance Chart						
Stent Diameter (mm)	NOMINAL					
	7 ATM	8 ATM	9 ATM†	10* ATM	11* ATM	12* ATM
3.0	2.8	2.9	3.0	3.1	3.1	3.2
3.5	3.3	3.4	3.5	3.6	3.7	3.8
4.0	3.8	3.9	4.0	4.1	4.2	4.3

* Beyond Rated Burst Pressure † Rated burst pressure

Note: Due to the semi-compliant nature of the balloon material, balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as specified on product label as this may result in a ruptured balloon with possible intimal damage and dissection.

Note: The nominal in vitro device specification does not take into account lesion resistance.

Note: Do not expand the stent beyond 4.3 mm.

10.8 Patient Information (United States only)

In addition to the Instructions for Use, the AVE Micro Stent® II Over-the-wire Coronary Stent System is packaged with additional specific information which include:

- A patient Implant card that includes both patient information and stent implant information. All patients will be instructed to keep this card in their possession at all times for procedure / stent identification.
- A Patient Teaching Guide which includes information on Arterial Vascular Engineering, the implant procedure and the AVE Micro Stent® II. (This accompanies the stent package, it is not provided in the package).
- A Device Tracking Form, (Device Registration Card and Device Explant Card) which will be completed by the hospital staff and forwarded to Arterial Vascular Engineering for the purposes of tracking all patients who have received a AVE Micro Stent® II, as required by Federal regulation.

DISCLAIMER OF WARRANTY

NOTE: ALTHOUGH THE STENT DELIVERY SYSTEM HEREAFTER REFERRED TO AS "PRODUCT" HAS BEEN MANUFACTURED UNDER CAREFULLY CONTROLLED CONDITIONS, ARTERIAL VASCULAR ENGINEERING, INCORPORATED (AVEI) HAS NO CONTROL OVER CONDITIONS UNDER WHICH THIS PRODUCT IS USED. AVEI, THEREFORE DISCLAIMS ALL WARRANTIES, BOTH EXPRESS AND IMPLIED, WITH RESPECT TO THE PRODUCT, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. AVEI SHALL NOT BE LIABLE TO ANY PERSON OR ENTITY FOR ANY MEDICAL EXPENSES OR ANY DIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES CAUSED BY ANY USE, DEFECT, FAILURE OR MALFUNCTION OF THE PRODUCT, WHETHER A CLAIM FOR SUCH DAMAGES IS BASED UPON WARRANTY, CONTRACT, TORT OR OTHERWISE NO PERSON HAS ANY AUTHORITY TO BIND AVEI TO ANY REPRESENTATION OR WARRANTY WITH RESPECT TO THE PRODUCT.

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PATENTS

Manufactured under one or more of the following United States Letters Patent: 5,292,331; 5,674,278. Other U.S. patents pending. Foreign patents granted and pending.

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AVE GFX™

OVER-THE-WIRE CORONARY STENT SYSTEM

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1. DEVICE DESCRIPTION

The AVE GFX™ Over-the-wire Coronary Stent System includes:

- A pre-mounted 316L stainless steel stent.
- A sheathless, Over-the-wire Coronary Stent System providing uniform, symmetrical stent deployment.
- Two radiopaque (gold) markers imbedded in the inner shaft beneath the balloon, proximal and distal to the stent. The markers are visible under fluoroscopy.
- Third and fourth shaft markers are located approximately 95cm and 105cm, respectively from the distal tip.

Figure 1. AVE GFX™ Graphic



Table 1. Device Specifications- GFX™

Stent Diameter	Stent Lengths	Minimum Guiding Catheter Inner Diameter*	Stent Deployment Pressure	Rated Burst Pressure	Stent Free Area %
3.0 mm	8,12,18,24 mm	0.064 inch	9 atm	9 atm	77
3.0 mm	30 mm	0.072 inch	9 atm	9 atm	77
3.5 mm	8,12,18,24 mm	0.064 inch	9 atm	9 atm	80
3.5 mm	30 mm	0.072 inch	9 atm	9 atm	80
4.0 mm	8,12,18,24,30 mm	0.072 inch	9 atm	9 atm	83

* See individual manufacture specifications for (Fr.) equivalent

2. INDICATIONS

The AVE GFX™ Over-the-wire Coronary Stent System is indicated for use in patients eligible for balloon angioplasty with symptomatic ischemic disease due to discrete *de novo* lesions in native coronary arteries (length \leq 30 mm) with a reference vessel diameter of 3.0 mm to 4.0 mm. Stenting is intended to improve coronary luminal diameter. (see Individualization of Treatment) Long term outcome (beyond 6 months) for this permanent implant is unknown at present.

3. CONTRAINDICATIONS

The AVE GFX™ Over-the-wire Coronary Stent System is contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.

- Patients who are judged to have a lesion that prevents complete inflation of an angioplasty balloon.

4. WARNINGS

- Since the use of this device carries the associated risk of subacute thrombosis, vascular complications and/or bleeding events, *judicious selection of patients is necessary.*
- Patients allergic to 316L stainless steel may suffer an allergic reaction to this implant.

5. PRECAUTIONS

(see also Individualization of Treatment)

- Only physicians who have received appropriate training should perform implantation of the stent.
- Stent placement should only be performed at hospitals where emergency coronary artery bypass graft surgery can be readily performed.
- Subsequent restenosis may require re-dilatation of the arterial segment containing the stent. The long-term outcome following such repeat dilatation of the coronary stents is unknown.
- When multiple stents are required, stent materials should be of similar composition.

5.1 Stent Handling – Precautions

- For single use only. Do not resterilize or reuse. Note product “Use By” date.
- The AVE GFX™ Over-the-wire Coronary Stent System is designed for use as a unit. The Stent is not to be removed from its delivery balloon. The AVE GFX™ Over-the-wire Coronary Stent System is not designed to be crimped onto another balloon. Removing the stent from its delivery balloon may damage the stent and/or lead to stent embolization.
- Special care must be taken not to handle or in any way disrupt the stent position on the delivery device. This is most important during catheter removal from packaging, placement over guidewire and advancement through hemostasis valve adapter and guiding catheter hub.
- Excessive manipulation, e.g., rolling the mounted stent may cause dislodgment of the stent from the delivery balloon.
- Use only the appropriate balloon inflation media. Do not use air or any gas medium to inflate the balloon as it may cause uneven expansion and difficulty in deployment of the stent.

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5.2 Stent Placement – Precautions

- Do not prepare or pre-inflate the balloon prior to stent deployment, other than as directed. Use balloon purging technique described in the Instructions for Use.
- Implanting a stent may lead to dissection of the vessel distal and/or proximal to the stented portion and may cause acute closure of the vessel requiring additional intervention (e.g., CABG, further dilation, placement of additional stents, or other).
- When treating multiple lesions, the distal lesion should be initially stented, followed by stenting of the proximal lesion. Stenting in this order obviates the need to cross the proximal stent when placing the distal stent and reduces the chances for dislodging the proximal stent.
- Do not expand the stent if it is not properly positioned in the vessel. (see Stent/System Removal-Precautions)
- Placement of the stent has the potential to compromise side branch patency.
- Balloon pressures should be monitored during inflation. Do not exceed rated burst pressure indicated on product label. (See Balloon Inflated Diameter dimensions in Table 6.) Use of pressures higher than those specified on product label may result in a ruptured balloon and potential intimal damage and dissection.
- Do not attempt to pull an unexpanded stent back through the guiding catheter, as dislodgment of the stent from the balloon may occur. (see Stent/System Removal-Precautions)
- Stent retrieval methods (use of additional wires, snares and/or forceps) may result in additional trauma to the vascular access site. Complications can include bleeding, hematoma or pseudoaneurysm.

5.3 Stent/System Removal- Precautions

Should unusual resistance be felt at any time, either during lesion access or during the removal of the Stent Delivery System post-stent implantation, the Stent Delivery System and the guiding catheter should be removed as a single unit. This must be done under direct visualization with fluoroscopy.

When removing the Stent Delivery System as a single unit:

- Do not pull the Stent Delivery System into the guiding catheter. Maintain guidewire placement across the lesion and carefully pull back the Stent Delivery System until the proximal balloon marker of the Stent Delivery System is aligned with the distal tip of the guiding catheter.

- The guiding catheter and Stent Delivery System should be carefully removed from the coronary artery as a single unit.
- The system should be pulled back into the descending aorta toward the arterial sheath. As the distal end of the guiding catheter enters into the arterial sheath, the catheter will straighten allowing safe withdrawal of the Stent Delivery System into the guiding catheter and the subsequent removal of the Stent Delivery System and the guiding catheter from the arterial sheath.
- Failure to follow these steps and/or applying excessive force to the Stent Delivery System can potentially result in loss or damage to the stent or Stent Delivery System components such as the balloon.

5.4 Post-Stent Placement – Precautions

- Care must be exercised when crossing a newly deployed stent with an intravascular ultrasound (IVUS) or a coronary guidewire, or a balloon catheter, to avoid disrupting the stent geometry.
- Do not perform Magnetic Resonance Imaging (MRI) scan on patients post-stent implantation until the stent has been completely endothelialized (eight weeks) to minimize the potential for migration. The stent may cause artifacts in MRI scans due to distortion of the magnetic field.

6. ADVERSE EVENTS

A total of 1084 patients were enrolled in three multi-center clinical trials to evaluate the safety and efficacy of the balloon expandable, AVE Micro Stent® II and GFX™ Over-the-wire Coronary Stent Systems for treatment of symptomatic coronary artery disease. Of these, 543 received the AVE Micro Stent® II, 210 received the AVE GFX™, and 331 received the JJIS Palmaz-Schatz® Stent while participating in the randomized SMART RCT Clinical Trial. These patients form the basis of the observed events reported (see Clinical Study). The GFX™ Registry enrolled two hundred ten (210) patients in a non-randomized, multi-center study. These patients form the basis for the observed events reported. (see Clinical Study)

Summary of Clinical Trial Patient Enrollment (n=1084)

	AVE Over-the-Wire Coronary Stent System	Palmaz-Schatz Coronary Stent- Control	Patient Totals
SMART Randomized Trial	AVE Micro Stent® II = 330	331	661
Feasibility Study	AVE Micro Stent® II = 213	NA	213
GFX Registry	AVE GFX™ = 210	NA	210
Patient Totals	753	331	1084

Sp

6.1 Observed Adverse Events

6.1.1 Randomized Clinical Trial and Feasibility Study

A total of 120 of 543 patients (22.1%) who received the AVE Micro Stent® II experienced one or more adverse events during the first 6 months of follow-up compared to 59 of 331 control patients (17.7%).

Table 2. Adverse Events During the First 6 Months

% [±95 % Confidence Interval] Number/Denominator

(n=874)

All Patients in SMART Trial :

543 AVE Micro Stent® II (213 feasibility + 330 randomized), 331 Palmaz-Schatz®.

SMART TRIAL		
	AVE Micro Stent® II (n=543)	Palmaz-Schatz® (n=331)
Death Total	1.7% [0.8%,3.1%] (9/543)	0.6% [0.1%,2.2%] (2/331)
Early (in-hospital)	0.6% [0.1%,1.6%] (3/543)	0.3% [0.0%,1.7%] (1/331)
Out-of -hospital	1.1% [0.4%,2.4%] (6/543)	0.3% [0.0%,1.7%] (1/331)
Q-wave MI Total	0.7% [0.2%,1.9%] (4/543)	0.6% [0.1%,2.2%] (2/331)
Early (in-hospital)	0.6% [0.1%,1.6%] (3/543)	0.6% [0.1%,2.2%] (2/331)
Out-of -hospital	0.2% [0.0%,1.0%] (1/543)	0.0% [0.0%,0.9%] (0/331)
Non-Q-wave Total	4.6% [3.0%,6.7%] (25/543)	3.9% [2.1%,6.6%] (13/331)
Early (in-hospital)	3.9% [2.4%,5.9%] (21/543)	3.3% [1.7%,5.9%] (11/331)
Out-of -hospital	0.7% [0.2%,1.9%] (4/543)	0.6% [0.1%,2.2%] (2/331)
CABG Total	3.9% [2.4%,5.9%] (21/543)	2.4% [1.0%,4.7%] (8/331)
Early (in-hospital)	1.3% [0.5%,2.6%] (7/543)	1.2% [0.3%,3.1%] (4/331)
Out-of -hospital	2.6% [1.4%,4.3%] (14/543)	1.2% [0.3%,3.1%] (4/331)
Stent Thrombosis Total	0.6% [0.1%,1.6%] (3/543)	0.6% [0.1%,2.2%] (2/331)
Early (in-hospital)	0.6% [0.1%,1.6%] (3/543)	0.3% [0.0%,1.7%] (1/331)
Out-of -hospital	0.0% [0.0%,0.6%] (0/543)	0.3% [0.0%,1.7%] (1/331)
Bleeding Requiring Transfusion-Procedural Vascular Complications	1.8% [0.9%,3.4%] (10/543)	1.5% [0.5%,3.5%] (5/331)
Cerebrovascular Accidents	5.5% [3.8%,7.8%] (30/543)	3.3% [1.7%,5.9%] (11/331)
Stent Delivery Failure	0.7% [0.2%,1.9%] (4/543)	0.0% [0.0%,0.9%] (0/331)
	2.5% [1.3%,4.1%] (14/543)	4.8% [2.8%,7.7%] (16/331)

*NOTE: * In cases where a patient experienced both an in-hospital event and an out-of-hospital event they are counted once in each group. They are counted only once in the event total. Hence, the sum of the in-hospital event rate and the out-of-hospital event rate may not equal the total event rate.*

Adverse event rates for the randomized patients in the SMART Trial (n=661) were not statistically different (p>0.01).

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A total of 9 of the 543 patients who received the AVE Micro Stent® II died during the clinical study. The 3 in-hospital deaths included one myocardial infarction at 192 hours after the stent placement and cardiac arrests occurring at 9 and 48 hours after stenting. The 6 out-of-hospital deaths occurred between 47 days and 244 days after stenting and were due to myocardial infarction (n=2), cardiac arrest (n=3), and pneumonia (n=1).

Stent thrombosis occurred in 0.6% of the patients who received the AVE Micro Stent® II. The incidence of vascular complications after stent placement was 5.5% (30/ 543) of the patients. The rate for procedural bleeding requiring transfusion was 1.8% (10/ 543) of the patients.

Initial delivery failure occurred in 2.5% (14/543) of the patients as follows: operator was unable to deliver first stent (n=7) and failure to deliver the assigned stent (n=7).

6.1.2 GFX™ Registry

A total of 14 of 210 patients (6.6%) who received the AVE GFX™ stent experienced one or more adverse events during the first 30 days of follow-up compared to 53 of 331 control patients (16%).

Table 3. Adverse Events at 30 Days
 % [\pm 95 % Confidence Interval] Number/Denominator
 (n=541)

	AVE GFX Stent™ N=210	Palmaz-Schatz® N=331
Death	0.5% [0.0%,2.6%] 1/210	0.3% [0.0%,1.7%] 1/331
In-Hospital	0.5% [0.0%,2.6%] 1/210	0.3% [0.0%,1.7%] 1/331
Out-of-hospital	0.0% [0.0%,1.4%] 0/210	0.0% [0.0%,0.9%] 0/331
Q-wave MI	0.0% [0.0%,1.4%] 0/210	0.6% [0.1%,2.2%] 2/331
In-Hospital	0.0% [0.0%,1.4%] 0/210	0.6% [0.1%,2.2%] 2/331
Out-of-hospital	0.0% [0.0%,1.4%] 0/210	0.0% [0.0%,0.9%] 0/331
Non Q-wave MI	2.9% [1.1%,6.1%] 6/210	3.9% [2.1%,6.6%] 13/331
In-Hospital	0.5% [0.0%,2.6%] 1/210	0.6% [0.1%,2.2%] 2/331
Out-of-hospital	2.4% [0.8%,5.5%] 5/210	3.3% [1.7%,5.9%] 11/331
CABG	0.0% [0.0%,1.4%] 0/210	1.2% [0.3%,3.1%] 4/331
In-Hospital	0.0% [0.0%,1.4%] 0/210	1.2% [0.3%,3.1%] 4/331
Out-of-hospital	0.0% [0.0%,1.4%] 0/210	0.0% [0.0%,0.9%] 0/331
Stent thrombosis	1.0% [0.1%,3.4%] 2/210	0.6% [0.1%,2.2%] 2/331
Bleeding (procedural transfusion)	0.0% [0.0%,1.4%] 0/210	1.5% [0.5%,3.5%] 5/331
Stroke	0.0% [0.0%,1.4%] 0/210	0.0% [0.0%,0.9%] 0/331
Vascular (local) complications	0.5% [0.0%,2.6%] 1/210	3.0% [1.5%,5.5%] 10/331
Stent Failures	1.9% [0.5%, 4.8%] 4/210	4.8% [2.8%,7.7%] 16/331

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A total of 1 of the 210 patients who received the AVE GFX™ stent died during the clinical study. The in-hospital death occurred 21 days after stenting and was due to cardiac arrest (n=1).

Stent thrombosis occurred in 1.0% of the patients who received the AVE GFX™ stent. The incidence of vascular complications of the stent placement was 0.5% (1/ 210) of the patients. The rate for procedural bleeding requiring transfusion was 0.0%.

Initial delivery failure occurred in 1.9% (4/ 210) of the patients as follows: operator was unable to deliver first stent (n=2), failure to deliver second stent (n=1), and failure to deliver third stent (n=1).

6.2 Potential Adverse Events

Adverse events (in alphabetical order) may be associated with the use of a coronary stent in native coronary arteries, (including those listed in Tables 2 and 3):

- Acute myocardial infarction
- Arrhythmia's, including VF and VT
- Death
- Dissection
- Drug reactions to antiplatelet agents/ contrast medium
- Emboli, distal (air, tissue or thrombotic emboli)
- Emergent Coronary Artery Bypass Surgery
- Hemorrhage, requiring transfusion
- Hypotension/Hypertension
- Infection and pain at the vascular access site
- Ischemia, myocardial
- Perforation
- Pseudoaneurysm , femoral
- Restenosis of stented segment
- Spasm
- Stent embolization
- Stent thrombosis/occlusion
- Stroke/Cerebrovascular Accidents
- Total occlusion of coronary artery

7. CLINICAL STUDY

A total of six hundred and sixty-one (661) patients were treated at forty (40) North American Investigational sites in SMART, a multi-center, randomized, prospective controlled clinical trial (RCT) in order to evaluate the safety and efficacy of the AVE Micro Stent® II (n=330) as compared to the JJIS Palmaz-Schatz® (n=331) stent in treating *de novo* and restenotic lesions in the native coronary arteries. A separate non-randomized feasibility study (n=213) was conducted prior to beginning the randomized trial. The primary end-point was defined as six-month clinically driven need for Target Lesion Revascularization (TLR)*. The GFX™ Registry enrolled a total of 210 patients. The JJIS Palmaz-Schatz® (n=331) stent was used as a retrospective control. The primary end point of the GFX™ Registry was defined as 30 day acute major events and success

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rates. A clinical events committee blinded to the treatment arm adjudicated all major clinical events and clinically driven TLR.

Eligibility was determined by the presence of angina or positive functional study (Exercise Treadmill Test). Patients were identified for elective stenting of *de novo* or restenotic lesions in native coronary arteries having vessel diameter between 3.0 mm and 4.0 mm with a lesion length of ≤ 30 mm, which could be covered by an appropriate length AVE Micro Stent® II (i.e., 6, 15 or 30 mm), or a combination thereof or an AVE GFX™ stent (i.e., 8, 18 or 30 mm) or a combination thereof. These patients underwent balloon angioplasty (1:1 balloon to artery ratio) after which a Stent Delivery System of the appropriate size was selected and deployed in the native coronary artery. Post deployment dilatation was performed utilizing a high-pressure balloon having a 1:1 balloon to artery ratio to obtain optimal stent apposition.

The anticoagulation regimen administered to 96.8% of the SMART RCT patients was 325 mg/day of uncoated, water-soluble aspirin for at least 6 months and ticlopidine 250mg twice a day for at least 14 days to 84% of the patients. At the discretion of the investigator, alternative therapy was allowed for non-optimal results, which were defined as > 30 mm stents implanted, $>10\%$ residual stenosis, any residual dissection, TIMI flow grade 0-1, or the presence of thrombus.

Clinical follow-up intervals for all treated SMART RCT patients were 30 days, 45 days, 6 months and 9 months. Follow-up for the GFX™ Registry patients was 30 days. A subset of patients underwent angiographic follow-up at 6 months for the SMART RCT. The study randomization was successful, within the SMART RCT, as both treatment groups were demographically equivalent. All treated randomized and non-randomized registry patients were included in the intent-to-treat efficacy analysis.

*TLR Definition

TLR is defined as a clinically driven repeat revascularization of a target lesion that was angiographically narrowed. The definition of "clinical driven" included a positive functional ischemia study, resting ischemia ECG changes in a distribution consistent with the target vessel, or ischemic symptoms and an angiographic minimal lumen diameter stenosis $\geq 50\%$ by QCA; revascularization of a target lesion with diameter stenosis $\geq 70\%$ by QCA without either angina or a positive functional study was also considered clinically driven.

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**Table 4. Principal Effectiveness and Safety Results
AVE Micro Stent® II (Randomized Control Trial) vs. Palmaz-Schatz® Stent
(N=661)**

Efficacy Measures	AVE Micro Stent II™ (N=330)	Palmaz-Schatz® (N=331)	Difference [95% C.I.]
Device Success by QCA	97.8% [95.5%,99.1%] (309/316)	95.2% [92.1%,97.3%] (295/310)	2.6% [-0.3%,5.5%]
Acute Procedural Success by QCA	94.1% [90.9%,96.4%] (301/320)	94.7% [91.6%,96.9%] (302/319)	-0.6% [-4.2%,3.0%]
Post Procedure In-Stent % DS Range (min,max)	5%±13% {-66%,100%} (316)	8%±12% {-30%,100%} (310)	-3.3% [-5.3%,-1.3%]
6 Months Follow-up In-Stent % DS Range (min,max)	37%±19% {-9%,80%} (101)	34%±20% {-10%,80%} (109)	3.7% [-1.6%,9.0%]
6 months Follow-up In-Stent Binary Restenosis rate	24.8% [16.7%,34.3%] (25/101)	22.9% [15.4%,32.0%] (25/109)	1.8% [-9.7%,13.4%]
TLR-free at 6 months* (K-M)	91.6% [88.2%,94.4%]	91.9% [89.0%,94.8%]	-0.3% [-4.6%,4.0%]
TVF-free at 6 months*(K-M)	85.8% [82.1%,89.5%]	87.7% [84.2%,91.2%]	-1.8% [-7.1%,3.4%]
Safety Measures and Other Clinical Events			
In-Hospital Clinical Events	6.4% [4.0%,9.6%] (21/330)	5.1% [3.0%,8.1%] (17/331)	1.2% [-2.3%,4.8%]
Out-of-Hospital Clinical Events	10.6% [7.5%,14.4%] (35/330)	9.7% [6.7%,13.4%] (32/331)	0.9% [-3.7%,5.5%]
Bleeding Complications	1.8% [0.7%,3.9%] (6/330)	1.5% [0.5%,3.5%] (5/331)	0.3% [-1.6%,2.3%]
Vascular Complications	3.6% [1.9%,6.3%] (12/330)	3.3% [1.7%,5.9%] (11/331)	0.3% [-2.5%,3.1%]
Stent Thrombosis	0.0% [0.0%,0.9%] (0/330)	0.6% [0.1%,2.2%] (2/331)	-0.6% [-1.4%,0.2%]
Survival at 30 days (K-M)	99.4% [98.0%,100%]	99.7% [99.3%,100%]	-0.3% [-1.0%,0.5%]
Survival at 180 days (K-M)	98.1% [96.7%,99.5%]	99.4% [98.6%,100%]	-1.3% [-2.9%,0.4%]
MACE rate at 6 month	16.1% [12.3%,20.5%] (53/330)	14.8% [11.2%,19.1%] (49/331)	1.3% [-4.3%,6.8%]
Hospitalization Post-Intervention (days)	1.55±2.04 [0,32] (330)	1.40±1.08 [0,11] (331)	0.1 [-0.1,0.4]

MACE: Major Adverse Cardiac Event (includes death, MI, and emergent CABG or target lesion revascularization).

TLR free: No target lesion revascularization.

TVF free: No death, any MI or target vessel revascularization.

QCA: Quantitative Coronary Angiography

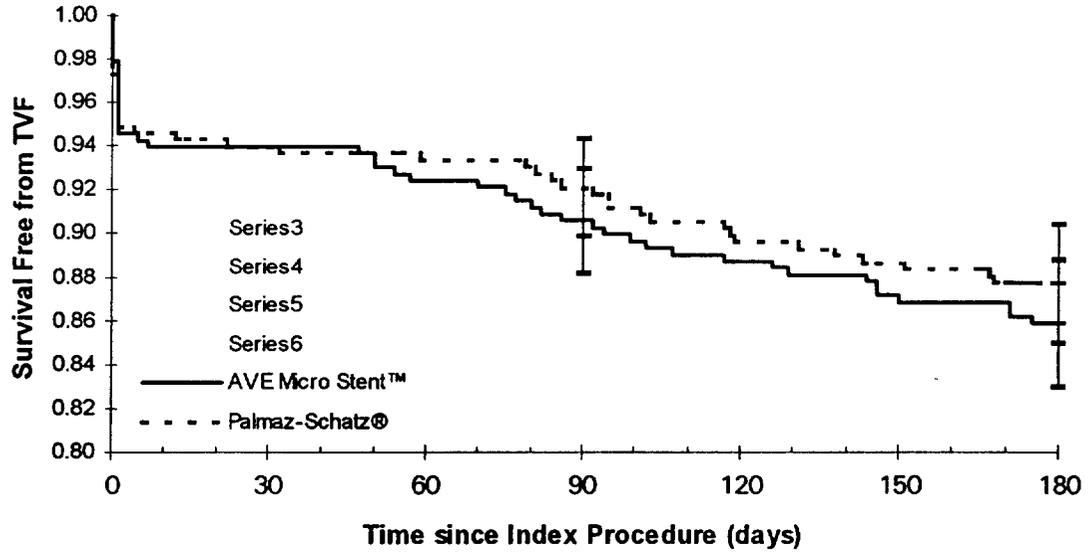
% DS: Diameter Stenosis

Stent Thrombosis: Stent thrombosis was defined as total thrombotic stent occlusion documented by angiography.

- In-hospital major clinical event: death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke prior to discharge, as determined by the independent Clinical Events Committee.
- Out-of-hospital major clinical event: death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke after discharge, as determined by the independent Clinical Events Committee.
- Bleeding complications: transfusions due to blood loss resulting from the percutaneous revascularization procedure.
- Device success: Attainment of <30% in-stent residual stenosis using the randomized treatment strategy only.
- Acute procedural success: <50% stenosis in-stent (or in-lesion if no in-stent measurement available) and freedom from in-hospital major adverse cardiac events (death, MI, emergent CABG, or repeat target lesion revascularization).

*Survival estimates by Kaplan-Meier method; Standard Error estimates by Greenwood formula

Figure 2. Freedom from Target Vessel Failure
All Randomized Patients Treated (N=661)



	Time after initial procedure (days)					
	0	7	14	30	90	180
AVE Micro Stent II™						
# At risk	323	308	308	307	293	256
# Events	7	20	20	20	31	46
Survived	97.9%	93.9%	93.9%	93.9%	90.5%	85.8%
% SE	0.8%	1.3%	1.3%	1.3%	1.6%	1.9%
Palmaz-Schatz®						
# At risk	322	310	309	307	295	256
# Events	9	18	19	20	26	40
Survived	97.3%	94.6%	94.3%	93.9%	92.1%	87.7%
% SE	0.9%	1.2%	1.3%	1.3%	1.5%	1.8%
Tests Between Groups						
	Test	Chi-Square	Deg Frdm	P-value		
	Log-Rank	0.27	1	0.60		
	Wilcoxon	0.29	1	0.59		

**Table 5. Principal Effectiveness and Safety Results
 AVE GFX™ Registry (N=210) vs. Palmaz-Schatz® Stent (N=331)
 AVE GFX™ Over-the-Wire
 Coronary Stent System**

Efficacy Measures	AVE GFX Stent™ (N=210)	Palmaz-Schatz® (N=331)	Relative Risk [95% C.I.]	Difference [95% C.I.]
Device Success (by QCA)	98.8% (162/164)	95.2% (295/310)	1.04 [1.00,1.08]	3.6% [0.7%,6.5%]
Acute Procedural Success (by QCA)	97.0% (159/164)	94.7% (302/319)	1.02 [0.98,1.07]	2.3% [-1.3%,5.9%]
Post Procedure In-Stent MLD (mm) Range (min,max)	2.92±0.44 (164) (1.68,3.95)	2.77±0.46 (310) (0.00,5.03)	N/A	0.15 [0.06,0.24]
Post Procedure In-Stent % DS Range (min,max)	4%±12% (164) (-30%,38%)	8%±12% (310) (-30%,100%)	N/A	-3.6% [-5.9%,-1.3%]
Safety Measures and Other Clinical Events				
In-Hospital MACE	3.3% (7/210)	5.1% (17/331)	0.65 [0.28,1.53]	-1.8% [-5.2%,1.6%]
In-Hospital Clinical Events	3.3% (7/210)	5.1% (17/331)	0.65 [0.28,1.53]	-1.8% [-5.2%,1.6%]
Out-of Hospital MACE (30 days)	0.5% (1/210)	0.9% (3/331)	0.53 [0.06,4.83]	-0.4% [-1.8%,1.0%]
Out-of-Hospital Clinical Events (30 days)	0.5% (1/210)	0.9% (3/331)	0.53 [0.06,4.83]	-0.4% [-1.8%,1.0%]
Bleeding Complications (30 days)	0.0% (0/210)	1.5% (5/331)	0.00 [0.00,0.00]	-1.5% [-2.8%,-0.2%]
Stroke (30 days)	0.0% (0/210)	0.0% (0/331)	- [-,-]	0.0% [-,-]
Vascular Complications (30 days)	0.5% (1/210)	3.0% (10/331)	0.16 [0.03,0.93]	-2.5% [-4.6%,-0.5%]
Stent Thrombosis	1.0% (2/210)	0.6% (2/331)	1.58 [0.23,10.94]	0.3% [-1.2%,1.9%]

Numbers are % (counts/sample size). CI = Confidence Interval.

Relative risk = AVE GFX™/Palmaz-Schatz® SE = $\sqrt{\{(1-p_1)/n_{11}+(1-p_2)/n_{21}\}}$ CI = RR*exp(±1.96*SE)

Difference = AVE GFX™/Palmaz-Schatz® SE = $\sqrt{\{p_1*q_1/n_1+p_2*q_2/n_2\}}$ CI = Diff±1.96*SE

Device success: Attainment of <30% in-stent residual stenosis using the assigned treatment strategy only.

Acute procedural success: <50% stenosis in-stent (or in-lesion if no in-stent measurement available) and freedom from in-hospital major adverse cardiac events (death, MI, emergent CABG or repeat target lesion revascularization).

In-hospital major clinical event: death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke, prior to discharge as determined by the independent Clinical Events Committee.

Out of hospital major clinical event: 30 day death, MI, emergent CABG, repeat target lesion revascularization, stent thrombosis, or stroke after discharge, as determined by the independent Clinical Events Committee.

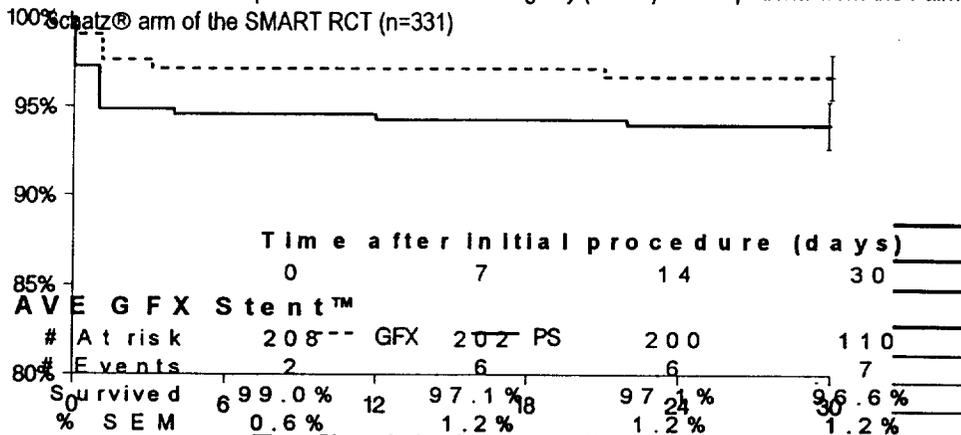
Bleeding complications: transfusions due to blood loss resulting from the percutaneous revascularization procedure.

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Figure 3. Freedom from Target Vessel Failure
 AVE GFX™ Registry vs. Palmaz-Schatz® stent (n=541)*

* n=541 combines all patients from the GFX™ Registry (n=210) and all patients from the Palmaz-Schatz® arm of the SMART RCT (n=331)

Survival Free from TVF



Time Since Index Procedure (days)				
	0	7	14	30
AVE GFX Stent™				
# At risk	208	202	200	110
# Events	2	6	6	7
Survived	99.0%	97.1%	97.2%	96.6%
% SEM	0.6%	1.2%	1.2%	1.2%
Palmaz-Schatz®				
# At risk	322	310	309	307
# Events	9	18	19	20
Survived	97.3%	94.6%	94.3%	93.9%
% SEM	0.9%	1.2%	1.3%	1.3%
Tests Between Groups				
	Test	Chi-Square	Deg FdM	P-value
	Log-Rank	2.90	1	0.09
	Wilcoxon	3.06	1	0.08

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8. INDIVIDUALIZATION OF TREATMENT

The risks and benefits described above should be carefully considered for each patient before use of the AVE GFX™ Over-the-wire Coronary Stent System. Patient selection factors to be assessed should include a judgment regarding risk of prolonged anticoagulation. Stenting is generally avoided in those patients at heightened risk of bleeding (e.g., those patients with recently active gastritis or peptic ulcer disease). (See Contraindications)

Premorbid conditions that increase the risk of poor initial results or the risks of emergency referral for bypass surgery (diabetes mellitus, renal failure, and severe obesity) should be reviewed.

Thrombosis following stent implantation is affected by several baseline angiographic and procedural factors. These include vessel diameter less than 3.0 mm, vessel thrombosis, poor distal flow and/or dissection following stent implantation. In patients that have undergone coronary stenting, the persistence of a thrombus or dissection is considered a marker for subsequent thrombotic occlusion. These patients should be monitored very carefully during the first month after stent implantation.

8.1 Use in Special Populations

The safety and effectiveness of the AVE GFX™ Over-the-wire Coronary Stent System has not been established for patients with any of the following characteristics:

- Patients with unresolved vessel thrombus at the lesion site.
- Patients with coronary artery reference vessel diameters < 3.0 mm.
- Patients with lesions located in the unprotected left main coronary artery, ostial lesions, or lesions located at a bifurcation.
- Patients with diffuse disease or poor outflow distal to the identified lesions.
- Patients with recent acute myocardial infarction where there is evidence of thrombus or poor flow.
- Patients with more than two overlapping stents due to risk of thrombus or poor flow.
- Patients with restenotic lesions.
- Patients for longer than 30 days follow-up.

The safety and effectiveness of using mechanical atherectomy devices (directional atherectomy catheters, rotational atherectomy catheters) or laser angioplasty catheters, to treat in-stent stenosis, has not been established.

9. HOW SUPPLIED

STERILE: This device is sterilized with e-beam radiation. It is intended for single use only. Non-pyrogenic. Do not use if package is opened or damaged.

CONTENTS: One (1) AVE GFX™ Over-the-wire Coronary Stent System.

STORAGE: Store in a cool, dry, dark place.

10. OPERATOR'S MANUAL

10.1 Inspection Prior to Use

Carefully inspect the sterile package before opening. It is not recommended that the product be used after the "Use By" date. If the integrity of the sterile package has been compromised prior to the product "Use By" date (e.g., damage of the package) contact your local AVE Representative for return information. Do not use if any defects are noted.

10.2 Materials Required

Quantity	Material
	Appropriate guiding catheter. (see Table 1- Device Specifications)
1	20 cc syringe.
	Normal heparinized saline.
1	0.014 inch x 300 cm guide wire.
1	Rotating hemostatic valve.
	Contrast medium diluted 1:1 with normal heparinized saline.
1	Inflation device.
1	Torque device.
Optional	Three-way stopcock.

10.3 Preparation

10.3.1 Guidewire Lumen Flush

Step	Action
1	Flush Stent Delivery System guidewire lumen with normal heparinized saline.
2	Remove protective tip covering the stent/balloon. Care should be taken not to disrupt the stent.
3	Verify that the stent is positioned between the proximal and distal balloon markers.

10.3.2 Balloon Preparation

Step	Action
1	Fill a 20 cc syringe with 5 cc of contrast/saline mixture (1:1).
2	Attach to delivery catheter and apply negative pressure for 20-30 seconds.
3	Slowly release pressure to allow negative pressure to draw mixture into balloon lumen.
4	Detach syringe and leave a meniscus of mixture on the hub of the balloon lumen.
5	Prepare inflation device in standard manner and purge to remove all air from syringe and

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	tubing.
6	Attach inflation device to balloon directly ensuring no bubbles remain at connection.
7	Leave on ambient pressure (neutral position). Note: Do not pull negative pressure on inflation device after balloon preparation and prior to delivering the stent.
8	Moisten the stent with normal heparinized saline by submerging the stent into a sterile bowl containing the solution. Note: Do not use gauze sponges to wipe down the stent as fibers may disrupt the stent.
9	Visually inspect the stent to ensure the stent is placed within the area of the proximal and distal balloon markers.
10	Check the integrity of the stent attachment on the delivery system by gently running the stent segment through the thumb and finger. If not intact, contact your AVE Representative and return the unused device to Arterial Vascular Engineering, Inc.

10.4 Delivery Procedure

Step	Action
1	Prepare vascular access site according to standard PTCA practice.
2	Pre-dilate the lesion/vessel with appropriate diameter balloon having a ratio of 1:1 with the diameter of the vessel.
3	Maintain neutral pressure on inflation device. Open rotating hemostatic valve to allow for easy passage of the stent. Note: If resistance is encountered, do not force passage. Resistance may indicate a problem and may result in damage to the stent if it is forced. Remove the system and examine.
4	Ensure guiding catheter stability before advancing the stent delivery system into the coronary artery.
5	Carefully advance the stent delivery system into the hub of the guiding catheter.
6	Note: If the physician encounters resistance to the stent delivery system prior to exiting the guiding catheter, do not force passage. Resistance may indicate a problem and may result in damage to the stent if it is forced. Maintain guidewire placement across the lesion and remove the stent delivery system as a single unit. (see Stent/System Removal - Precautions)
7	Advance delivery system over the guidewire to the target lesion under direct fluoroscopic visualization. Utilize the proximal and distal radiopaque markers on the balloon as a reference point. If the position of the stent is not optimal, it should be carefully repositioned or removed. (see Stent/System Removal - Precautions) Expansion of the stent should not be undertaken if the stent is not properly positioned in the target lesion segment of the vessel.
8	Optimal stent placement requires the distal end of the stent to be placed approximately 1 mm beyond the distal end of the lesion.
9	Sufficiently tighten the rotating hemostatic valve. Stent is now ready to be deployed.

10.5 Deployment Procedure

Step	Action
1	Deploy stent by inflating balloon to nominal pressure to expand the stent. Note: Refer to product labeling and Table 6 for the proper inflation pressure. Do not exceed Rated Burst Pressure.
2	Maintain inflation pressure for 15-30 seconds for full expansion of the stent.
3	Note: Under-expansion of the stent may result in stent movement. Care must be taken to properly size the stent to ensure the stent is in full contact with the arterial wall upon deflation of the delivery system balloon.

10.6 Removal Procedure

Step	Action
1	Deflate the balloon by pulling negative pressure on the inflation device. Allow adequate time, at least 15 seconds, for full balloon deflation. Longer stents may require more time for deflation.
2	Fully open the hemostatic valve.
3	Maintain position of guiding catheter and guidewire to prevent the guiding catheter from being drawn into vessel. Very slowly, withdraw the balloon from the stent maintaining negative suction, allowing movement of the myocardium to gently dislodge the balloon from stent.
4	Tighten the hemostatic valve.
5	Repeat angiography and visually assess the vessel and the stent for proper expansion.
6	A second balloon inflation may be required to ensure optimal stent expansion. In such instances, a non-compliant, higher-pressure balloon of adequate size (the same size as the stent delivery system balloon or larger) and length may be used to accomplish this. Note: In smaller or diffusely diseased vessels, the use of high balloon inflation pressures may over-expand the vessel distal to the stent and could result in vessel dissection. Do not expand stent beyond 4.3 mm.
7	The final internal stent diameter should be equal to or slightly larger than the proximal and distal reference vessel diameters.
8	Repeat angiography to evaluate and determine procedure status or termination. Note: Should the need arise for placement of a second stent to adequately cover the lesion length, placement of the stent most distal in the artery should be done prior to placement of the proximal stent, if possible.
9	Note: Observation of the patient and angiographic evaluation of the stent site should be performed periodically within the first 30 minutes after stent placement. If stent placement is associated with the onset of thrombus or suspected thrombus in the region of the stented segment, intracoronary infusions of a thrombolytic agent is recommended.

10.7 *in vitro* Information

Table 6. Stent Diameter (mm) at Deployment Pressure (ATM) Compliance Chart

AVE GFX™ Over-the-wire Coronary Stent System Stent Diameter (mm) at Deployment Pressure (ATM) Compliance Chart						
Stent/ Balloon Diameter (mm)	Nominal					
	7 ATM	8 ATM	9 ATM†	10* ATM	11* ATM	12* ATM
3.0	2.8	2.9	3.0	3.1	3.1	3.2
3.5	3.3	3.4	3.5	3.6	3.7	3.7
4.0	3.8	3.9	4.0	4.1	4.2	4.3

* Beyond Rated Burst Pressure † Rated burst pressure

Note: Due to the semi-compliant nature of the balloon material, balloon pressures should be monitored during inflation. Do not exceed rated burst pressure as specified on product label as this may result in a ruptured balloon with possible intimal damage and dissection.

Note: The nominal *in vitro* device specification does not take into account lesion resistance.

Note: Do not expand the stent beyond 4.3 mm.

10.8 Patient Information (United States only)

In addition to the Instructions for Use, the AVE GFX™ Over-the-wire Coronary Stent System is packaged with additional specific information which include:

- A Patient Implant Card that includes both patient information and stent implant information. All patients will be instructed to keep this card in their possession at all times for procedure/stent identification.
- A Patient Guide which includes information on Arterial Vascular Engineering, the implant procedure and the AVE GFX™ Over-the-wire Coronary Stent System. (This accompanies the stent package; it is not provided in the package.)
- A Device Tracking Form, (Device Registration Form and Device Explant Form) which will be completed by the hospital staff and forwarded to Arterial Vascular Engineering for the purposes of tracking all patients who have received an AVE GFX™ Over-the-wire Coronary Stent System, as required by Federal regulation.

DISCLAIMER OF WARRANTY

NOTE: ALTHOUGH THE STENT DELIVERY SYSTEM HEREAFTER REFERRED TO AS "PRODUCT" HAS BEEN MANUFACTURED UNDER CAREFULLY CONTROLLED CONDITIONS, ARTERIAL VASCULAR ENGINEERING, INCORPORATED (AVEI) HAS NO CONTROL OVER CONDITIONS UNDER WHICH THIS PRODUCT IS USED. AVEI, THEREFORE DISCLAIMS ALL WARRANTIES, BOTH EXPRESSED AND IMPLIED, WITH RESPECT TO THE PRODUCT, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. AVEI SHALL NOT BE LIABLE TO ANY PERSON OR ENTITY FOR ANY MEDICAL EXPENSES OR ANY DIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES CAUSED BY ANY USE, DEFECT, FAILURE OR MALFUNCTION OF THE PRODUCT, WHETHER A CLAIM FOR SUCH DAMAGES IS BASED UPON WARRANTY, CONTRACT, TORT OR OTHERWISE NO PERSON HAS ANY AUTHORITY TO BIND AVEI TO ANY REPRESENTATION OR WARRANTY WITH RESPECT TO THE PRODUCT.

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PATENTS

Manufactured under one or more of the following United States Letters Patent: 5,292,331; 5,674,278. Other U.S. patents pending. Foreign patents granted and pending.

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