Summary of Safety and Effectiveness Data

1.0 General Information

Device Generic Name:	TIPS Endoprosthesis
Device Trade Name:	GORE VIATORR TIPS Endoprosthesis
Applicant's Name and Address:	W.L. Gore & Associates, Inc. 3450 West Kiltie Lane Flagstaff, AZ 86001
Date of Panel Recommendation:	None
PMA Application Number:	P040027
Date of Notice of Approval to Applicant:	December 6, 2004

2.0 Indication for Use

The GORE VIATORR TIPS Endoprosthesis is indicated for use in *de novo* and revision treatment of portal hypertension and its complications such as variceal bleeding, gastropathy, ascites, and/or hepatic hydrothorax.

3.0 Contraindications

There are no known contraindications for this device.

4.0 Warnings and Precautions

See Warnings and Precautions in the labeling (Instructions for Use).

5.0 Device Description

The GORE VIATORR TIPS Endoprosthesis is intended to be used to create or revise a transjugular intrahepatic portosystemic shunt ("TIPS"). The VIATORR TIPS Endoprosthesis is delivered to the liver via percutaneous access from the jugular vein through a 10 Fr hemostatic introducer sheath. Once delivered, the device serves as a shunt between the portal and hepatic veins.

The VIATORR TIPS Endoprosthesis is comprised of an implantable prosthesis ("VIATORR Endoprosthesis") and a catheter delivery system ("VIATORR Delivery System"). The catheter delivery system consists of deployment line, constraining sleeve, delivery catheter, and access sleeve.

The VIATORR Endoprosthesis consists of a self-expanding nitinol (nickel-titanium) stent that supports an expanded polytetrafluoroethylene (ePTFE) graft (please refer to Figure 1). The endoprosthesis is divided into two regions: an unlined portal region, and an ePTFE-lined intrahepatic region. The lined region consists of a porous, ePTFE inner base tube and an impermeable outer wrap of ePTFE/FEP. The base tube is optimized for blood flow, and the outer wrap minimizes the permeation of thrombogenic mucin and

bile into the blood-contacting surface, as well as minimizes tissue attachment to the lined region from the surrounding vessel. The anticipated purpose of the lining is to reduce tissue ingrowth, which is often responsible for loss of patency in bare metal stents. The interface between the lined and unlined regions is indicated by a circumferential radiopaque gold marker band. An additional radiopaque gold marker is located on the trailing edge of the device. Endoprosthesis diameters and lengths are provided in Table 1.

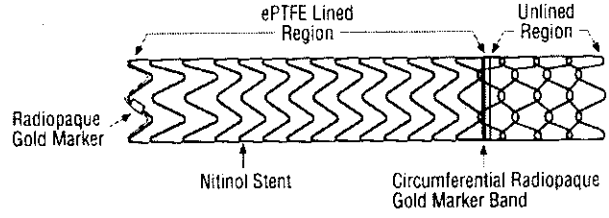
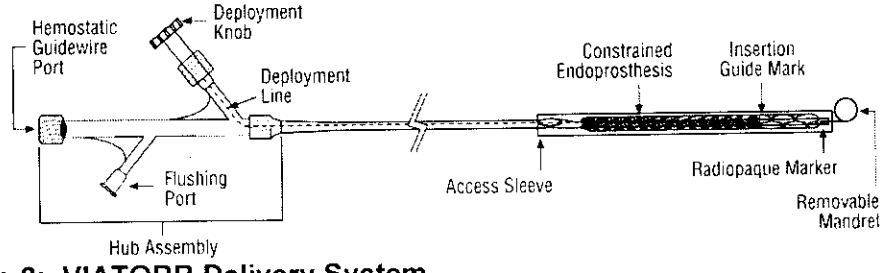


Figure 1: VIATORR Endoprosthesis

The endoprosthesis is secured to the leading end of a dual-lumen delivery catheter beneath the constraining sleeve and a protective plastic access sleeve (please refer to Figure 2). The access sleeve facilitates insertion of the delivery catheter through the hemostasis valve of an introducer sheath. A mark on the access sleeve serves as a guide to confirm correct insertion depth. The delivery catheter is compatible with a ≤ 0.038" (0.97 mm) diameter guidewire, and has a working length of 75 cm. A radiopaque marker is located beneath the leading tip of the delivery catheter. A removable ePTFE constraining sleeve is used to constrain and subsequently deploy the graft-lined region of the VIATORR Endoprosthesis. An extension of the constraining sleeve becomes the deployment line, which is routed through the catheter shaft and allows for the deployment of the device. The trailing end of the delivery catheter is attached to a hub assembly that includes a central hemostatic guidewire port, a flushing port, and a port for the deployment line/ deployment knob. The delivery catheter is packaged with a stainless steel mandrel inserted into the leading edge of the guidewire lumen that must be removed prior to use.



5.1. **Figure 2: VIATORR Delivery System**

Table 1: VIATORR Endoprosthesis Sizes

Part Number	Diameter (mm)	Total Length (cm)	Lined Length† (cm)	Unlined Length‡ (cm)
PTB084275	8 mm	6 cm	4 cm	2 cm
PTB085275	8 mm	7 cm	5 cm	2 cm
PTB086275	8 mm	8 cm	6 cm	2 cm
PTB087275	8 mm	9 cm	7 cm	2 cm
PTB088275	8 mm	10 cm	8 cm	2 cm
PTB104275	10 mm	6 cm	4 cm	2 cm
PTB105275	10 mm	7 cm	5 cm	2 cm
PTB106275	10 mm	8 cm	6 cm	2 cm
PTB107275	10 mm	9 cm	7 cm	2 cm
PTB108275	10 mm	10 cm	8 cm	2 cm
PTB124275	12 mm	6 cm	4 cm	2 cm
PTB126275	12 mm	8 cm	6 cm	2 cm
PTB128275	12 mm	10 cm	8 cm	2 cm

† Lined length refers to the graft-lined intrahepatic region (see Figure 1).
‡ Unlined length refers to the "chain-link" portal region.

6.0 Alternative Practices or Procedures

The goal of any treatment modality is to reduce the portal pressure gradient and to prevent or treat any complications or manifestations of portal hypertension.

6.1. Medical / Endoscopic Treatments

Several systemic pharmaceutical agents can be used to lower portal pressures in patients with portal hypertension including Nonselective β–blockers and Nitrates, and Octreotide.

Several devices are available to treat the local *complications* of portal hypertension including transoral inflatable esophageal balloons, sclerosing agents, or band ligation for bleeding varices. Ascites can be treated with intermittent paracentesis or a permanent shunt which drains fluid from the peritoneal cavity into a main vascular duct.

6.2. Surgical Procedures

The past creation of surgical vascular anastomotic shunts using grafts has been performed to reduce portal hypertension and provide alternative conduits to the systemic circulation. These included the following:

1. Portacaval shunt (PCS)- Splenic vein to the inferior vena cava (IVC)
2. Mesocaval shunt - Superior mesenteric vein (SMV) to the IVC
3. Splenorenal shunt - Splenic vein to the left renal vein.

7.0 Marketing History

The GORE VIATORR TIPS Endoprosthesis has been commercially available throughout the world, including Europe, Asia, Latin America, and Australia, since 1999. There are no countries in which the device has been withdrawn from marketing for any reason related to safety or effectiveness.

8.0 Potential Adverse Effects of the Device on Health

In the pivotal study to assess the safety and effectiveness of the GORE VIATORR TIPS Endoprosthesis, 125 subjects received the VIATORR device. A total of 295 adverse events were reported in 96 subjects. Table 2 summarizes many of the adverse events in subjects receiving the VIATORR device during this trial.

Table 2: Adverse Events Reported for VIATORR Group

Adverse Event	# Subjects (%) / # Events
Encephalopathy	47 (37.6%)/54
Ascites	26 (20.8%)/27
Hydrothorax	11 (8.8%)/12
Anemia	11 (8.8%)/11
GI Other/Bile Duct	11 (8.8%)/12
PSG>12mmHg	10 (8.0%)/11
Fever	10 (8.0%)/10
Lower Extremity Edema	8 (6.4%)/8
Pulmonary Failure	7 (5.6%)/7
Hypotension	7 (5.6%)/8
Renal Dysfunction	6 (4.8%)/7
Pneumonia	6 (4.8%)/6
Urinary Tract Infection	6 (4.8%)/7
Myocardial Infarction	6 (4.8%)/6
Cardiac Other	6 (4.8%)/8
Sepsis	5 (4.0%)/ 5
Liver Failure	5 (4.0%) /5
Coagulopathy	5 (4.0%)/ 6
Other Infection	5 (4.0%)/ 5
Bowel Other	5 (4.0%)/5
Upper GI Bleed	4 (3.2%)/4
Liver Other	4 (3.2%)/4
Congestive Heart Failure	4 (3.2%)/4
Electrolyte Imbalance	4 (3.2%)/4
Spontaneous Bacterial Peritonitis	3 (2.4%)/3
Stenosis	3 (2.4%)/3
Hepatic Vein Stenosis	3 (2.4%)/3
Pulmonary Edema	3 (2.4%)/3
Prosthesis Malposition	2 (1.6%)/2
Occlusion	2 (1.6%)/2
Shock	2 (1.6%)/2

Adverse Event	# Subjects (%) / # Events
Renal Other	2 (1.6%)/2
Lung Other	2 (1.6%)/2
Hepatic Infarction	2 (1.6%)/2
Variceal Bleed	1 (0.8%)/2
Prosthesis Migration	1 (0.8%)/1
Hemoperitoneum	1 (0.8%)/1
Liver Cancer	1 (0.8%)/1
Hemolysis	1 (0.8%)/1
Multiorgan Failure	0 (0.0%)/0
Non-Variceal Bleed	0 (0.0%)/0

Further discussion of adverse events can be found in this document in the sections "Safety Results (Adverse Events)" and "Serious Events".

9.0 Summary of Preclinical Studies

9.1. Biocompatibility

Biocompatibility testing was conducted for the VIATORR TIPS Endoprosthesis (i.e., VIATORR Endoprosthesis and VIATORR Delivery System). The purpose of this testing was to verify that the materials and processes used to manufacture the VIATORR TIPS Endoprosthesis resulted in devices with acceptable biocompatibility. Testing was conducted in accordance with Federal Good Laboratory Practices per 21 CFR§58. According to ISO 10993-1, the VIATORR TIPS Endoprosthesis is classified as an implant device with permanent blood contact. The VIATORR Delivery System is classified as an externally communicating device with limited exposure (≤ 24 hours) and circulating blood contact. Both the implant and the delivery system passed all tests.

The VIATORR Endoprosthesis is made of expanded polytetrafluoroethylene (ePTFE), fluorinated ethylene propylene (FEP), gold, and nickel-titanium alloy ("nitinol"). Historically, ePTFE, FEP, nitinol, and gold have been characterized as safe biomaterials. Literature reviews have documented that these materials have an acceptable long term history of human implantation.

The materials used to manufacture the delivery system are commonly used in other commercially available medical devices, such as percutaneous transluminal coronary angioplasty (PTCA) catheters, peripheral transluminal angioplasty (PTA) catheters, and ePTFE sutures. The materials in these devices have been documented and have been demonstrated to be safe to use in limited-duration, blood-contacting medical devices. No component of the delivery system is intended to have greater than limited (≤ 24 hours) contact with the patient.

Table 3 summarizes the biocompatibility test results for the implant. Table 4 summarizes the biocompatibility test results for the catheter.

Table 3: Summary of Biocompatibility Test Results for the Implant

Test Name	Test Method	Results
Cytotoxicity	L929 MEM Elution Test – ISO	No biological reactivity
Sensitization	Kligman Maximization Test – ISO	Non-sensitizing
Irritation/ Intracutaneous Reactivity	Intracutaneous Injection Test – ISO	Negligible irritant
Acute Systemic Toxicity	Systemic Injection Test – ISO	No significantly greater biological reaction than the controls.
Pyrogenicity	Rabbit Pyrogen Test (Material Mediated) – ISO	Non-pyrogenic
Hemocompatibility	Hemolysis – Rabbit Blood – ISO	Non-hemolytic
Subchronic Toxicity	14 Day Repeat Dose Intravenous Toxicity Study – (Subchronic) – ISO	Not toxic
Genotoxicity/ Mutagenicity	*Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay – ISO	Non-mutagenic
Implantation	Short Term Intramuscular Implantation Test (14 Days) – ISO	Non-toxic
	Short Term Intramuscular Implantation Test (28 Days) – ISO	Non-toxic

Table 4: Summary of Biocompatibility Test Results for the Delivery System

Test Name	Test Method	Results
Cytotoxicity	L929 MEM Elution Test – ISO	Non-cytotoxic
Sensitization	Kligman Maximization Test – ISO	Non-sensitizing
Irritation/ Intracutaneous Reactivity	Intracutaneous Injection Test – ISO	Negligible irritant
Acute Systemic Toxicity	Systemic Injection Test – ISO	Non-toxic
Pyrogenicity	Rabbit Pyrogen Test (Material Mediated) – ISO	Non-pyrogenic
Hemocompatibility	Hemolysis – Rabbit Blood – ISO	Non-hemolytic

All test results indicate that the materials and processes used to manufacture the VIATORR TIPS Endoprosthesis and VIATORR Delivery System are biocompatible and suitable for their intended use.

9.2. In Vitro Preclinical Testing

In vitro testing was performed on the VIATORR TIPS Endoprosthesis and its delivery system and was consistent with the requirements of ISO 25539-1, *Cardiovascular implants – Endovascular devices – Part 1: Endovascular prostheses*. Although this

standard is not focused directly on a stent-graft used for TIPS, many of the key attributes described in the ISO standard are relevant to the VIATORR TIPS Endoprosthesis and its intended clinical application.

The express intent of this *in vitro* testing was to verify that the performance attributes of the VIATORR TIPS Endoprosthesis are sufficient to minimize the risk of adverse events under anticipated clinical use conditions. Results obtained from the *in vitro* test regimen provide evidence substantiating the safety and effectiveness of the device.

A summary of results is presented below for each of the *in vitro* tests. Table 6 summarizes test results associated with the functional requirements of the delivery system, and Table 7 summarizes test results related to functional requirements of the endoprosthesis or implant.

The results of the *in vitro* testing demonstrate that the VIATORR TIPS Endoprosthesis meets established functional requirements for endovascular prostheses. Furthermore, these data substantiate the safety and effectiveness of the device which, consequently, is expected to perform as intended when used in accordance with its labeled indications.

Please refer to Tables 6 and 7 for a summary of the *in vitro* testing conducted on the device.

Table 6: Summary of *In Vitro* Test Results Related to Functionality of the VIATORR Delivery System

Test	Relevant Functional Attribute	Summary of Test Results
Delivery System Torquability	• Ability to access the intended location • Ability to deploy the implant • Ability to retract delivery system	Sterilized, finished delivery systems were subjected to a clinically relevant amount of torquing and were deployed in a clinically relevant *in vitro* TIPS model. All tested delivery systems were deployed successfully.
Delivery Catheter Bond Strength	• Ability to access the intended location • Ability to deploy the implant • Ability to retract delivery system	The longitudinal tensile strength of the critical bonds and joints of the VIATORR delivery catheter were determined. Results indicate that there is at least 95% confidence level that the minimum tensile strength of each critical catheter junction will exceed the ISO 10555-1 standard for the respective bond.
Deployment Knob/Line Assembly Tensile Strength	• Ability to deploy the implant	The tensile strength of the catheter deployment knob/line assembly was determined to demonstrate conformance to design requirements. There is at least 95% confidence that any individual deployment knob/line tensile strength exceeds the 95% upper prediction value for Deployment Force.
Delivery Catheter Length	• Ability to access the intended location	The minimum and maximum expected catheter working lengths for final sterilized delivery catheters tested met the established design specifications at a minimum confidence level of 95%.

Test	Relevant Functional Attribute	Summary of Test Results
Delivery System Accessory Compatibility	• Ability to access the intended location • Ability to deploy the implant • Ability to retract delivery system	Sterilized final devices were tested for dimensional compatibility; all tested samples successfully passed the guidewire through the lumen and were able to be passed through the appropriately sized introducer sheath. All tested samples were dimensionally compatible with the recommended guidewire and introducer sheath per established design specifications.
Delivery System Deployment Force	• Ability to deploy the implant	The force required to deploy the VIATORR Endoprosthesis was determined. The maximum expected deployment force does not exceed the minimum expected strength of the deployment knob/line tensile strength.
Delivery System Deployment Reliability	• Ability to access the intended location • Ability to deploy the implant • Ability to retract delivery system	Final, sterilized devices, including appropriate introducer sheaths, guidewires, and balloon catheters, were used and deployed in a clinically relevant *in vitro* TIPS model. All devices were deployed successfully. Binomial statistics demonstrate high reliability with a 95% confidence level that the devices will access the intended implant location, safely deploy the implant, and be successfully withdrawn when used in a manner consistent with labeling or under anticipated clinical use.
Delivery Catheter Burst	• Ability to access the intended location	This test evaluated the burst strength of sterilized final devices for conformance to established performance specifications. The minimum burst pressure exceeded the acceptance criterion, demonstrating that there is at least 95% confidence that any individual catheter burst pressure is in excess of the acceptance criterion.
Delivery System Radiopacity	• Ability to access the intended location • Ability to deploy the implant • Ability to retract delivery system • Fluoroscopic visualization	Tissue density was simulated by aluminum plates of varying densities. A digital fluoroscope was used for imaging. The results of the *in vitro* radiopacity testing show that the radiopacity of the delivery systems have sufficient radiopacity for clinical use.
Catheter Leak	• Hemostasis	This test evaluated leak resistance of the delivery system hub for conformance with established performance specifications. No leakage occurred in any test when pressurized up to 20 atm, demonstrating conformance to the appropriate design specifications and ISO 10555-1.

Table 7: Summary of *In Vitro* Test Results Related to Functionality of the VIATORR TIPS Endoprosthesis

Test	Relevant Functional Attribute	Summary of Test Results
Endoprosthesis Respiratory Fatigue	• Fixation effectiveness of the implant • Durability and integrity of the implant	Respiratory fatigue resistance was evaluated for 10 years of simulated physiological loading (67.5 million cycles) under "worst-case" test conditions. The model simulated the respiratory movement imposed upon the liver and subsequent loading of a shunt device with the intent of quantifying these effects on the endoprosthesis. The results of this test indicated that the endoprosthesis was not adversely affected by 10 years of simulated cyclic loading expected to be induced by the diaphragm.
Endoprosthesis Radial Compression Strength	• Fixation effectiveness of the implant • Durability and integrity of the implant • Appropriate sizing of the implant • Patency of the implant	This test characterized the force required to radially compress the device. All device diameters were tested. The radial compression strengths of the device are anticipated to be adequate for clinical use.
Endoprosthesis Finite Element Analysis	• Durability and integrity of the implant	The location and magnitude of the maximum, mean, and alternating strains in the VIATORR TIPS Endoprosthesis nitinol wire frame were analytically determined as a function of radial compression when subjected to catheter loading and an *in vivo* pulsatile loading environment. Peak strain magnitudes at simulated catheter loading are predicted to be below the ultimate tensile strain of the nitinol wire.
Corrosion	• Durability and integrity of the implant	The corrosion susceptibility of the endoprosthesis was analyzed using potentio-dynamic polarization testing in a simulated *in vivo* environment (Phosphate-Buffered Saline, pH 7.4, at 37°C). The average breakdown potential for the VIATORR device was not statistically different from the average breakdown potential for the control device at a 95% confidence level. In addition, explanted devices were examined for evidence of nitinol corrosion and abrasion. There was no evidence of corrosion or abrasion on any of the explanted devices. In addition, the nitinol wire was in excellent condition in all cases.
Endoprosthesis Longitudinal Tensile	• Durability and integrity of the implant	The longitudinal tensile strength of final sterilized VIATORR devices was characterized in a manner consistent with ISO 7198:1998. All diameters were tested and showed acceptable tensile strength, exceeding the minimum design requirements with at least 95% confidence.

Test	Relevant Functional Attribute	Summary of Test Results
Endoprosthesis Burst Strength	• Durability and integrity of the implant	Burst strength of final sterilized VIATORR devices was characterized, and testing was performed in a manner consistent with ISO 7198:1998. All diameters were tested and showed acceptable burst strength, exceeding the minimum design requirements with at least 95% confidence. The minimum expected burst pressure is greater than the pressures typically used for post-deployment balloon touch-up.
Endoprosthesis Liner to Stent Attachment Peel Strength	• Durability and integrity of the implant	The strength of the attachment between the stent frame component and the graft liner component was characterized. Testing indicated that there was acceptable bonding of the two materials.
Nitinol Mechanical Properties	• Durability and integrity of the implant	This testing was performed to assess the mechanical behavior of the nitinol wire used in the VIATORR device. Test articles were taken from each wire diameter used, and were exposed to all applicable processes used in the production of the body of the stent-graft. Material characteristics were recorded, including ultimate tensile strength and elongation at break.
Nitinol Material Analysis	• Durability and integrity of the implant	The bulk material and surface of the nitinol wire used for the VIATORR device were chemically analyzed and quantified. The surfaces of the wire were also examined under SEM to detect defects and contamination. The bulk material analysis and surface analysis met design requirements. Surface observations with SEM demonstrated a consistently smooth wire surface with no unacceptable anomalies such as pitting, cracks, or contaminants.
Endoprosthesis Integral Water Permeability	• Permeability considerations	The integral water permeability of the VIATORR device was evaluated for all three diameters in a manner consistent with ISO 7198:1998. Final sterilized devices were tested, and the quantity and nature of the leak was reported for each sample.
Endoprosthesis Microscopic Determination of Porosity	• Permeability considerations • Patency of the implant	The fibril length of the ePTFE graft component was determined in a manner consistent with ISO 7198:1998. The results conform to the stated design requirement.
Endoprosthesis Fluid Entry Pressure	• Permeability considerations	This test was conducted to characterize the water and bile entry pressures of the graft liner component. Testing was performed in a manner consistent with ISO 7198:1998, and indicated that the graft liner component is capable of resisting bile and water pressures greater than those seen in the vasculature without fluid permeation.
Endoprosthesis Length	• Appropriate sizing of the implant	This test characterized the usable length of the VIATORR device post-deployment in final sterilized devices as compared to the applicable design specifications. All devices tested met the acceptance criteria .

Test	Relevant Functional Attribute	Summary of Test Results
Endoprosthesis Diameter and Wall Thickness	• Appropriate sizing of the implant	The inner and outer diameters and wall thickness of deployed devices were characterized and verified in a manner consistent with ISO 7198:1998. Final sterilized devices were measured. All devices met their respective acceptance criteria with at least 95% confidence.
Endoprosthesis Bend Radius	• Patency of the implant	The bend radii (without kinking) of each VIATORR device diameter (final sterilized devices tested for each diameter) were characterized. All sizes of the device met the requirements for bend radius, with at least 95% confidence, indicating that the endoprosthesis is expected to have sufficient flexibility for its intended use.
Stent Free Surface Area Calculation	• Patency of the implant	Calculations were performed to determine the stent free (or unsupported) surface area as a function of the device's compressed diameter.
Endoprosthesis Magnetic Resonance Imaging Safety	• MRI Compatibility	The VIATORR TIPS Endoprosthesis is not anticipated to present a hazard or additional risk to an implant recipient or individual undergoing an MR procedure using an MR system operating with a shielded, static magnetic field of 1.5 Tesla or less. The device has therefore been determined to be "MR safe" under these conditions.
Endoprosthesis Radiopacity	• Ability to accurately deploy the implant • Fluoroscopic visualization	Tissue density was simulated by aluminum plates of varying densities. A digital fluoroscope was used for imaging. The results of the *in vitro* radiopacity testing show that the radiopacity of the endoprosthesis is sufficient for clinical use.
Delivery System Deployment Reliability	• Ability to accurately deploy the implant • Durability and integrity of the implant	Final, sterilized devices, including appropriate introducer sheaths, guidewires, and balloon catheters, were used and deployed in a clinically relevant *in vitro* TIPS model. All devices were deployed successfully, and were examined post-deployment. All implants were intact and exhibited no signs of damage. Binomial statistics demonstrate high reliability with a 95% confidence level that the devices will accurately deploy, and the implant will maintain its durability and integrity when used in a manner consistent with labeling or under anticipated clinical use.

9.3. Sterilization, Packaging and Shelf Life

The GORE VIATORR® TIPS Endoprosthesis is sterilized using a validated 100% Ethylene Oxide cycle in accordance with ANSI/AAMI/ISO guidelines. The validations were performed utilizing a mass overkill sterilization methodology consisting of three half cycles and one full cycle, which provides a minimum of 12 logs of reduction to the Process Challenge Device. The sterilization process has been shown to be acceptable for sterilization to a minimum SAL of 10^{-6}.

The GORE VIATORR® TIPS Endoprosthesis is supplied sterile in a protective tray. Packaging consists of four components: tray, primary pouch, secondary pouch, and shipping box.

The GORE VIATORR® TIPS Endoprosthesis has a 3-year shelf life.

9.4. In Vivo Preclinical Testing

Two preclinical *in vivo* studies were conducted to evaluate the performance of the VIATORR TIPS Endoprosthesis. The purpose of these studies was to evaluate the safety and performance of the VIATORR Endoprosthesis in an *in vivo* environment that modeled the clinical application (i.e., *de novo* and revision transjugular intrahepatic portosystemic shunt or TIPS). The studies were intended to demonstrate the safety of the device prior to beginning human clinical studies and employed a porcine model. This animal model was used to assess the ability of the delivery system to successfully access the target site, deploy the endoprosthesis and be withdrawn from the vasculature, and to assess functionality, luminal patency, physiological effects, and biological response to the implanted endoprostheses. Please refer to Table 5.

Table 5: Summary of Preclinical *In Vivo* Studies of the VIATORR TIPS Endoprosthesis Conducted by Gore

Animal Study	#/ Type of Animal	Test Article	Methods	Results/ Conclusions
Chronic Study of TIPS Endoprosthesis for TIPS Revision	9 minipigs	Human size prototype device and delivery system	Catheter delivery and device functionality were assessed chronically for TIPS revision in 9 animals (three animals each were maintained in life for approximately 30-days, 60-days, and 90-days).	All devices were successfully delivered and deployed. The functional requirements were met. All devices were patent at retrieval, and the host tissue response was judged to be acceptable at both gross and histological examination. There was no evidence of device/ component migration or graft disruption. These results support the clinical use of the device for TIPS revision.
Chronic Study of TIPS Endoprosthesis for *de novo* TIPS	13 minipigs	Human size device and delivery system	Catheter delivery and device functionality were assessed sub-chronically and chronically for *de novo* TIPS in 13 animals. Six animals were maintained in life for approximately 30-days, three animals for approximately 60-days, and four animals for approximately 90-days.	All TIPS Endoprostheses were successfully delivered and deployed. The functional requirements were met. All devices were patent at retrieval, and the host tissue response was judged to be acceptable at both gross and histological examination. There was no evidence of device/ component migration or graft disruption. These results support the clinical use of the device for *de novo* TIPS.

10.0 Summary of Clinical Studies

10.1. Objectives

The objectives of the clinical studies were to assess the safety and effectiveness of the GORE VIATORR TIPS Endoprosthesis in the *de novo* and/or revision treatment of portal hypertension and its complications such as variceal bleeding, gastropathy, ascites, and/or hepatic hydrothorax.

Three studies were performed to evaluate the safety and effectiveness of the VIATORR device.

Training Cases	2 VIATORR learning cases at each institution (28 total).
De Novo Study	253 subjects randomized to VIATORR or Control device.
Revision Study	28 *De Novo* subjects requiring revision prior to or at 6 months.

10.2. *De Novo* Study

This was a multicenter, randomized, controlled trial with 253 subjects being randomized to undergo a *de novo* TIPS procedure with either the GORE VIATORR TIPS Endoprosthesis or a Commercially available TIPS Endoprosthesis (Control). Subjects were eligible for enrollment and randomization if the following major criteria were met.

Main Inclusion Criteria

1. Complications of portal hypertension refractory to or intolerant of conventional therapies in patients with native/transplanted livers or in patients with occluded pre-existing TIPS or occluded surgical shunts.
2. Age at least 18 and a candidate for conventional treatment.

Main Exclusion Criteria

1. Mental status grade 3 or 4.
2. Serum Cr > 2.0 mg/dL, bilirubin > 3.0 mg/dL, INR> 1.8, Hgb < 8.0 g/L.
3. Systolic blood pressure < 80 mmHg.
4. MI within 3 months of *de novo* procedure.
5. Hemodialysis or peritoneal dialysis.
6. Active infection or biliary obstruction.
7. Hepatic malignancy or polycystic liver disease.
8. Budd-Chiari syndrome.
9. Any of the following *during* the procedure:
    a. Venographic % DS > 50% or occlusion of the portal or hepatic veins.
    b. Gastric varices due to splenic vein thrombosis.
    c. Intrahepatic tract connecting portal and hepatic veins cannot be created.
    d. Pre-existing TIPS or surgical shunt in which the pre-TIPS venography demonstrates blood flow through the shunt.

The primary effectiveness endpoint of this study was *primary stent patency at 6 months* as defined by both PSG ≤ 12 mmHg *and* percent diameter stenosis (%DS) ≤ 50% with no reintervention(s) to maintain or re-establish patency. A failure of any of these criteria

was considered a loss of primary patency. The primary safety endpoint was the type and rates of adverse events. Multiple secondary endpoints were evaluated including:

1. Technical success (delivery and deployment).
2. Hemodynamic success post-procedure (Post-procedure PSG ≤ 12 mmHg).
3. Venographic success post-procedure (Post-procedure % DS ≤ 30%).
4. Time to return of original symptoms (Event-free survival).
5. Primary assisted patency (Patency but intervention had been performed prior).
6. Secondary patency (Time to complete occlusion, despite reintervention).
7. Time to Loss of Patency.
8. Changes in Portosystemic Pressure Gradient (PSG).
9. Time to First Reintervention or Revision.
10. Time to Death.

Prophylactic antibiotics were administered to all subjects prior to stent placement and the TIPS tract was created based on standard institution procedures. Following the placement of the stent, subjects underwent follow-up procedures according to Table 8. An independent radiographic Core Lab was used to evaluate angiographic outcomes.

Table 8: Subject Follow-up Procedures in *De Novo* Study

	Post-Procedure	Discharge	1 Month	3 Months	6 Months
Physical Exam		X	X	X	X
Blood Tests		X	X	X	X
Child-Pugh		X	X	X	
Mental Status		X	X	X	X
Shunt Venography	X				X
Pressure Gradient Measurements	X				X
Color Doppler Ultrasound		X	X	X	X
Adverse Events	X	X	X	X	X

Baseline subject and treatment characteristics are shown in Table 9.

Table 9: Baseline Subject and Treatment Characteristics

Parameter	VIATORR Group (N = 125)	Control (N = 128)	p-value
Gender			0.002*
Male	93 (74.4%)	71 (55.5%)	
Female	32 (25.6%)	57 (44.5%)	
Age			0.971‡
Mean (years)	53	54	
Ethnicity			0.778†
White or Caucasian	96 (76.8%)	98 (76.6%)	
Hispanic or Latino	18 (14.4%)	22 (17.2%)	
Black or African American	4 (3.2%)	2 (1.6%)	
American Indian or Alaska Native	0 (0.0%)	1 (0.8%)	
Asian	1 (0.8%)	0 (0.0%)	
Pacific Islander or Hawaii Native	0 (0.0%)	1 (0.8%)	
Other	1 (0.8%)	0 (0.0%)	
Unknown	5 (4.0%)	4 (3.1%)	

Parameter	VIATORR Group (N = 125)	Control (N = 128)	p-value
Primary Indication			0.467†
Variceal Bleeding	45 (36.0%)	45 (35.2%)	
Ascites	72 (57.6%)	76 (59.4%)	
Gastropathy	3 (2.4%)	0 (0.0%)	
Hepatic Hydrothorax	4 (3.2%)	4 (3.1%)	
Other	1 (0.8%)	3 (2.3%)	
Liver Disease Etiology			
Hepatitis B	11 (8.8%)	7 (5.5%)	0.337*
Hepatitis C	59 (47.2%)	56 (43.8%)	0.615*
Alcoholic Cirrhosis	79 (63.2%)	60 (46.9%)	0.011*
Cryptogenic	13 (10.4%)	23 (18.0%)	0.105*
Other	17 (13.6%)	21 (16.4%)	0.599*
Comorbidities			
Hepatic Failure	20 (16.0%)	21 (16.4%)	1.000*
Pulmonary Hypertension	0 (0.0%)	3 (2.3%)	0.247*
Renal Failure	0 (0.0%)	3 (2.3%)	0.247*
Pulmonary Edema	1 (0.8%)	1 (0.8%)	1.000*
Child-Pugh Class			0.611‡
A	14 (11.2%)	15 (11.7%)	
B	85 (68.0%)	91 (71.1%)	
C	23 (18.4%)	20 (15.6%)	
Unable to calculate	3 (2.4%)	2 (1.6%)	
Mental Status Score			0.191‡
0	100 (80.0%)	110 (85.9%)	
1	20 (16.0%)	16 (12.5%)	
2	3 (2.4%)	2 (1.6%)	
3	1 (0.8%)	0 (0.0%)	
4	1 (0.8%)	0 (0.0%)	
MELD Score			0.737‡
6 – 10	47 (37.6%)	42 (32.8%)	
11 – 15	61 (48.8%)	64 (50.0%)	
16 – 20	13 (10.4%)	18 (14.1%)	
21 – 24	2 (1.6%)	1 (0.8%)	
Unable to calculate	2 (1.6%)	3 (2.3%)	

* p-values based on 2 by 2 Fisher's Exact Test to compare percentages between treatment groups.
‡ p-values based on Wilcoxon Rank Sum Test to compare the two treatment groups.
† p-values based on Fisher's Exact Test to compare distribution across categories between the two treatment groups.

There was no difference between groups in procedure time, fluoroscopic time or contrast injection volume. The 10mm stents accounted for most stents deployed - 78.8% in the VIATORR group and 67.8% in the Control group.

10.2.1. Subject Accountability

A total of 125 subjects were enrolled in the VIATORR arm and 128 in the Control arm. One subject randomized to the VIATORR group mistakenly received the Control device due to investigator error. General subject follow-up accountability is shown in Table 10.

Table 10: Subject Accountability

	VIATORR Group (N = 125)	Control Group (N = 128)	p-values
Subject Disposition			
Number Completed	85 (68.0%)	70 (54.7%)	0.039
Number Withdrawn	40 (32.0%)	58 (45.3%)	
Reason for Withdrawal			
Death	18 (14.4%)	22 (17.2%)	0.607
Liver Transplant	13 (10.4%)	16 (12.5%)	0.694
Lost to Follow-Up	6 (4.8%)	1 (0.8%)	0.064
Revision	3 (2.4%)	14 (10.9%)	0.010
Subject Choice / Other	0 (0.0%)	5 (3.9%)	0.060

10.2.2. Effectiveness Results

Primary Patency at 6 Months. (PSG ≤ 12 mmHg *and* %DS ≤ 50% without reintervention)

Three distinct analyses for the primary effectiveness endpoint were performed.

1. Intent to Treat Analysis (ITT)

   Included *all* enrolled subjects according to the randomized assignment. Subjects without complete evaluation at 6 months were endpoint failures.

2. Modified Intent to Treat Analysis (MITT)

   Included all enrolled subjects according to the randomized assignment. Subjects who died or received transplants prior to the 6-month follow-up were excluded from the evaluation.

3. As Treated/Evaluable per Protocol (AT)

   A subset of subjects who completed the study (based on device received) and was evaluated for effectiveness at the 6-month study endpoint or who had documented failure of primary patency prior to 6 months. Subjects lost to death/transplant or with incomplete 6-month data were not included. However, if 1 of the 2 primary assessments was performed and a failure at 6 months, that subject was included.

The primary effectiveness results based on each of the 3 analyses are provided in Table 11.

Table 11: Results of Primary Patency Analyses

	ITT		MITT		AT	
	VIATORR Group	Control Group	VIATORR Group	Control Group	VIATORR Group	Control Group
N	126	127	98	94	80	71

	ITT		MITT		AT	
	VIATORR Group	Control Group	VIATORR Group	Control Group	VIATORR Group	Control Group
Primary Patency Success	57 (45.2%)	28 (22.0%)	57 (58.2%)	28 (29.8%)	57 (71.3%)	28 (39.4%)
Primary Patency Failure	69 (54.8%)	99 (78.0%)	41 (41.8%)	66 (70.2%)	23 (28.8%)	43 (60.6%)

The p-value for rates of primary patency in all three analyses was <0.001. There was no relationship between the primary outcome and any baseline variables. Although subjects with a primary indication of variceal bleeding had a higher percentage of successful outcomes versus those with ascites, this was not statistically significant.

The reasons for failure to achieve the primary endpoint are provided in the Table 12.

Table 12: Reasons for Failure to Achieve Primary Patency in Each Analysis

	ITT		MITT		AT	
	VIATORR Group	Control Group	VIATORR Group	Control Group	VIATORR Group	Control Group
N	69	99	41	66	23	43
PSG > 12 and/or %DS > 50	15 (11.9%)	19 (15.0%)	15 (15.3%)	19 (20.2%)	14 (17.5%)	20 (28.2%)
Reintervention	6 (4.8%)	9 (7.1%)	6 (6.1%)	9 (9.6%)	6 (7.5%)	9 (12.7%)
Incomplete Evaluation	11 (8.7%)	18 (14.2%)	11 (11.2%)	18 (19.1%)	---	---
Enrolled into Revision Arm	3 (2.4%)	14 (11.0%)	3 (3.1%)	14 (14.9%)	3 (3.8%)	14 (19.7%)
Transplant	11 (8.7%)	13 (10.2%)	---	---	---	---
Death	17 (13.5%)	20 (15.7%)	---	---	---	---
Other	0 (0.0%)	5 (3.9%)	0 (0.0%)	5 (5.3%)	---	---
Lost to F/U	6 (4.8%)	1 (0.8%)	6 (6.1%)	1 (1.1%)	---	---

It should be noted that 3 VIATORR subjects and 5 Control subjects who died or received a transplant were not excluded from the MITT analysis because they were known to have failed the primary patency evaluation at a time prior to the 6 month assessment. These 8 subjects were therefore included as device failures in the MITT analysis.

10.2.3. Secondary Effectiveness Evaluations

Several parameters were evaluated immediately post-procedure as secondary endpoints including technical success (delivery and deployment), hemodynamic success (PSG ≤ 12 mmHg), and venographic success (%DS ≤ 30%). Success rates are shown below in Table 13.

Table 13: Results of Secondary Effectiveness Evaluations

	VIATORR Group	Control Group
Technical Success	125/125 (100%)	128/128 (100%)
Hemodynamic Success	104/110 (94.5%)	110/119 (92.4%)
Venographic Success	120/125 (96.0%)	114/125 (91.2%)

All subjects who failed the strict hemodynamic success criteria had significant reductions in PSG post-procedure with a mean reduction on the order of 42-44%.

Time to Return of Symptoms

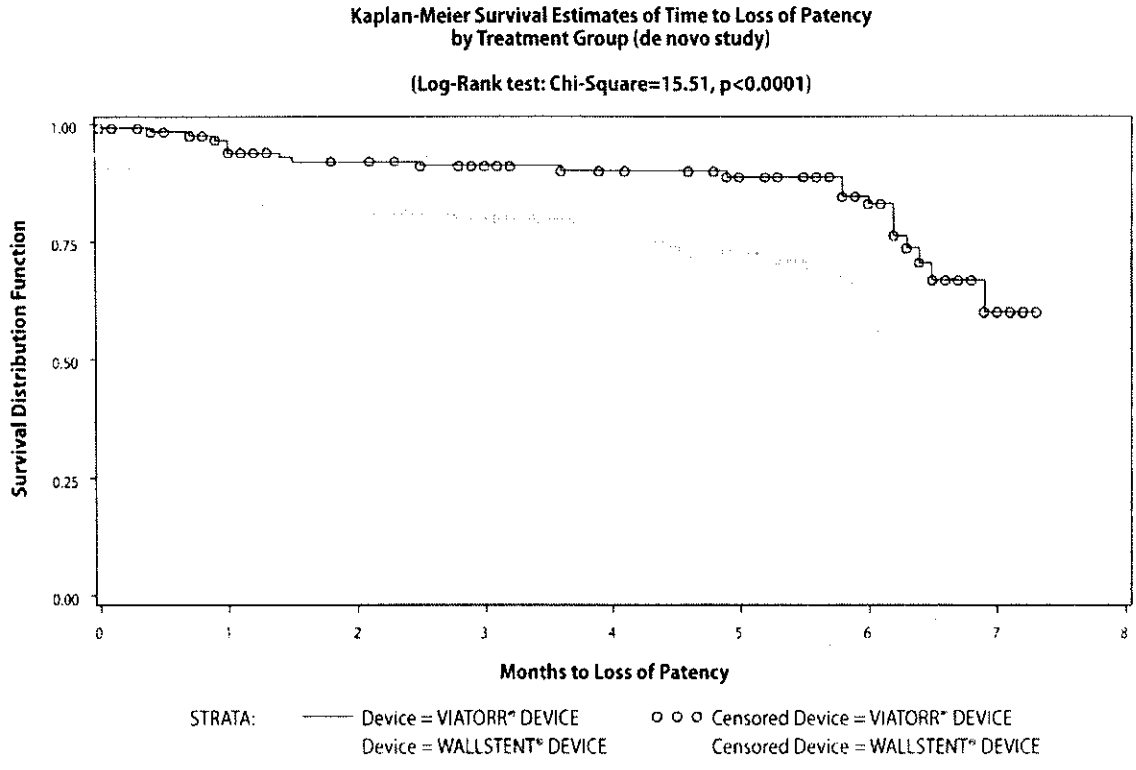
There was no significant difference between groups for the time to return of symptoms for which the TIPS was primarily performed (p=0.77). The estimated probability of remaining free from symptoms throughout the 6-month study interval was 56.1% (95% CI: 46.7%; 65.5%) for the VIATORR group and 59.0% (95% CI: 49.0%; 68.9%) for the Control Group. The estimated probability of no early (< 30 days) return of symptoms was also similar between the groups: 75.2% versus 75.9% respectively.

Primary Assisted Patency and Secondary Patency

Two subjects in each group met the definition of primary assisted patency at 6 months. One subject in the VIATORR group and 3 in the Control Group met the definition of secondary patency (all due to procedure-related thrombosis).

Patency

The probability of maintaining patency through 6 months was 60% (95% CI: 42.6%, 77.5%) for the VIATORR group versus 22.7% (95% CI: 6.5%, 39.0%) for the Control Group (p<0.001). Time to loss of patency is demonstrated in the Kaplan-Meier estimate as follows.



Reinterventions to Maintain or Re-establish Patency

A total of 55 reinterventions were performed in 52 subjects to maintain or re-establish patency prior to or immediately following the primary evaluation at the 6-month visit. Table 14 summarizes the number of reinterventions in the two groups.

Table 14: Reinterventions to Maintain or Re-establish Patency

		VIATORR Group	Control Group
Timing of Reintervention	Prior to 6 Month Assessment	8	22
	Immediately after 6 Month Assessment	8	17
	TOTAL	**16**	**39**
Reason for Reinterventions	PSG > 12mmHG only	11	12
	% DS > 50% only	1	3
	PSG > 12mmHg and % DS>50%	1	19
	PSG > 12 mmHg and % DS unknown	1	2
	Neither	2	3
	TOTAL	**16**	**39**
Types of Reinterventions	Balloon dilation only	7	10
	Balloon dilation and Placement of additional device	2	8
	Other device placed No balloon dilation	1	0
	Parallel TIPS with Control device	1	0

		VIATORR Group	Control Group
	Revision with VIATORR device	5	21
	TOTAL	**16**	**39**

The difference in number of subjects requiring a reintervention was significant ($p<0.001$) between the two groups as was the difference in time to reintervention ($p=0.007$). At 30 days, the probability of freedom from reintervention or revision was 96.7% for the VIATORR group and 88.9% for the Control Group. At 6 months, these probabilities were 92.0% and 79.5% respectively.

Other Effectiveness Endpoints

Table 15 summarizes the results of other effectiveness evaluations performed.

Table 15: Results of Other Effectiveness Analyses

	VIATORR Group	Control Group
Mean % DS at Primary Evaluation	16.4%	42.4%
Mean % DS Change (Time of Primary Evaluation versus Procedure Completion)	2.3%	23.5%
Subjects with reported stenotic lesions by Core Lab at Primary Patency Evaluation (Subjects with stenotic lesions in tract only)	76.9% (32.1%)	95.7% (55.7%)
Hemodynamic Success (PSG ≤ 12 mmHg) at Evaluation of Primary Patency	76.1% (54/71)	48.5% (33/68)
Mean PSG at Primary Patency Evaluation	10.2 mmHg	13.6 mmHg
Mean % PSG Reduction versus Baseline	44.8%	31.6%
% Change in MELD Score 6 months versus pre-procedure	21.0%	15.3%

10.2.4. Gender Bias

The *de novo* subject cohort was comprised of 65% males and 35% females. Although no subject selection bias was noted in this multicenter, randomized, controlled trial, when stratified by gender, a greater percentage of males (74.4%) were assigned to the VIATORR device group than females (25.6%).

This distribution difference is similar to and supported by current literature for randomized TIPS studies cited in the PMA. In these randomized studies, the overall study enrollment was 30.3 – 79.2% for males randomized to a TIPS treatment and 37.9 – 74.3% for those males receiving the control therapy. Conversely, the overall range for female participants was 20.8 – 69.7% for those receiving a TIPS and 25.7 – 62.1% for those randomized to the control group.

Despite this disproportionate distribution, both gender groups displayed similar results in the ITT analysis of primary patency. In the VIATORR group, the overall percentage of success was 45.2% (44.7% males and 46.9% females were reported to have a successful outcome). In the Control Group, the overall percentage of success was 22.0% (18.6% males and 26.3% females reported as having a successful outcome).

10.2.5. Safety Results (Adverse Events)

A total of 615 adverse events in 203 subjects were reported in the *de novo* study. Ninety-six (96) of the 125 VIATORR subjects (76.8%) and 107 of the 128 Control subjects (83.6%) experienced at least one adverse event. There was no difference between the groups in the number of adverse events per subject. Of the 615 events, 328 occurred early (≤ 30 days) and the remaining 287 events occurred after 30 days. Table 16 summarizes adverse events which occurred in ≥ 2% of those receiving the VIATORR device.

Table 16: Reported Adverse Events

Adverse Event	VIATORR Group (N=125)	Control Group (N=128)
Encephalopathy	47 (37.6%)	54 (42.2%)
Ascites	26 (20.8%)	25 (19.5%)
Hydrothorax	11 (8.8%)	6 (4.7%)
Anemia	11 (8.8%)	10 (7.8%)
GI Other/Bile Duct	11 (8.8%)	3 (2.3%)
PSG>12mmHg	10 (8.0%)	26 (20.3%)
Fever	10 (8.0%)	5 (3.9%)
Lower Extremity Edema	8 (6.4%)	8 (6.3%)
Pulmonary Failure	7 (5.6%)	4 (3.1%)
Hypotension	7 (5.6%)	1 (0.8%)
Renal Dysfunction	6 (4.8%)	8 (6.3%)
Pneumonia	6 (4.8%)	4 (3.1%)
Urinary Tract Infection	6 (4.8%)	2 (1.6%)
Myocardial Infarction	6 (4.8%)	2 (1.6%)
Cardiac Other	6 (4.8%)	6 (4.7%)
Sepsis	5 (4.0%)	4 (3.1%)
Liver Failure	5 (4.0%)	10 (7.8%)
Coagulopathy	5 (4.0%)	2 (1.6%)
Other Infection	5 (4.0%)	9 (7.0%)
Bowel Other	5 (4.0%)	8 (6.3%)
Upper GI Bleed	4 (3.2%)	0 (0.0%)
Liver Other	4 (3.2%)	2 (1.6%)
Congestive Heart Failure	4 (3.2%)	4 (3.1%)
Electrolyte Imbalance	4 (3.2%)	3 (2.3%)
Spontaneous Bacterial Peritonitis	3 (2.4%)	2 (1.6%)
Stenosis	3 (2.4%)	33 (25.8%)
Hepatic Vein Stenosis	3 (2.4%)	3 (2.3%)
Pulmonary Edema	3 (2.4%)	1 (0.8%)

Only 42 events in 33 subjects were considered by the investigator to be device-related as illustrated in the Table 17.

Table 17: Device-Related Adverse Events

Device-Related Event	VIATORR Group	Control Group
Stenosis	1	17
PSG > 12 mmHg	3	11
Occlusion	1	2

Device-Related Event	VIATORR Group	Control Group
Congestive Heart failure	1	0
Fever	1	0
Ascites	0	2
Hemolysis	0	1
Prosthesis Malposition	0	1
Hepatic Vein Stenosis	0	1
TOTAL	7 events in 7 subjects	35 events in 26 subjects

10.2.6. Serious Events

A total of 247 adverse events were characterized as serious including 119 events in 61 VIATORR subjects and 128 events in 65 Control subjects. These are presented below in Table 18. A subject may have been counted twice if he or she experienced the adverse events both prior to day 30 and after day 30.

Table 18: Serious Adverse Events

	Early (≤ 30 days)		Late (> 30 days)	
	VIATORR Group (N=125)	Control Group (N=128)	VIATORR Group (N=117)	Control Group (N=109)
Death	2 (1.6%)	5 (3.9%)	16 (13.7%)	17 (15.6%)
Encephalopathy	29 (23.2%)	33 (25.8%)	22 (18.8%)	24 (22.0%)
Other Infections	6 (4.8%)	8 (6.3%)	10 (8.5%)	6 (5.5%)
Pulmonary Edema / Failure	5 (4.0%)	4 (3.1%)	4 (3.4%)	1 (0.9%)
Myocardial Infarction	4 (3.2%)	2 (1.6%)	2 (1.7%)	0 (0.0%)
Renal Insufficiency / Acute Renal Failure	4 (3.2%)	8 (6.3%)	5 (4.3%)	5 (4.6%)
Hepatic Infarction	2 (1.6%)	0 (0.0%)	0(0.0%)	0 (0.0%)
Sepsis	1 (0.8%)	2 (1.6%)	4 (3.4%)	3 (2.8%)
Liver Failure	1 (0.8%)	8 (6.3%)	4 (3.4%)	2 (1.8%)
Hemoperitoneum	1 (0.8%)	3 (2.3%)	0 (0.0%)	0 (0.0%)
Spontaneous Bacterial Peritonitis	1 (0.8%)	2 (1.6%)	2 (1.7%)	0 (0.0%)
Congestive Heart Failure	0 (0.0%)	2 (1.6%)	4 (3.4%)	2 (1.8%)
Shock	0 (0.0%)	1 (0.8%)	2 (1.7%)	0 (0.0%)
Multiorgan Failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

With the exception of liver failure within 30 days (p=0.036), there were no statistically significant differences between the groups.

10.2.7. Algorithm-Generated Adverse Event Analysis

This analysis was performed to examine several specific events based on laboratory-based algorithms. As seen in Table 19 there were no significant differences between the groups at the 6-month follow-up time.

Table 19: Algorithm-Generated Adverse Events

	VIATORR Group	Control Group
Liver Failure	0.0% (0/74)	1.6% (1/61)
Worsening Liver Disease	13.7% (10/73)	15.5% (9/58)
Renal Dysfunction	2.6% (2/77)	1.6% (1/63)

10.2.8. Deaths and Survival

Forty (40) subjects died while enrolled in the *de novo* study, 18 in the VIATORR group and 22 in the Control Group (p=0.607). Most (82.5%) occurred > 30 days after the procedure. No death was determined to be device-related.

Estimates of 30 day survival were similar between groups (97.5% for the VIATORR group, and 94.9% for the Control Group) as were estimates of probability for survival throughout the course of the study (69.7% for the VIATORR group, and 73.8% for the Control Group).

10.2.9. Transplants

Twenty-nine (29) subjects received transplants while enrolled in the *de novo* study, 13 VIATORR subjects (10.4%) and 16 Control subjects (12.5%, p=0.694). Although 10 of the 29 subjects were documented to be asymptomatic at the time of transplant, the sponsor was unable to assess patency consistently in subjects who were taken to transplantation.

10.2.10. Change in Mental Status and Hepatic Encephalopathy

One month following the TIPS procedure, 18.9% of evaluable VIATORR subjects and 14.7% of Control subjects had a mental status score that was worse than baseline score. Evaluable subjects are those with a one-month evaluation and who were not withdrawn during the one-month evaluation period.

At 6 months, this was 2.5% of the evaluable VIATORR subjects and 9.4% of the evaluable Control subjects. Evaluable subjects are those with a six-month evaluation and who were not withdrawn during the course of the six-month follow-up period. At 6 months, most of the subjects in the VIATORR group (95%) and the Control Group (89%) had a mental status score of zero and all had scores of ≤ 2. Of the subjects who died prior to the 6 month follow-up, 17 had symptoms of hepatic encephalopathy at the time of death (6 being VIATORR subjects and 11 being Control subjects).

Reported adverse events for encephalopathy post-*de novo* TIPS were 37.56% and 42.2% in the VIATORR Device and Control Device groups, respectively, during the course of the six-month follow-up period. Twenty-nine (23.2%) VIATORR Device and 33 (25.8%) Control Device subjects had an early (≤ 30 days) adverse event of encephalopathy reported (p=0.663). Late (> 30 days) adverse events for encephalopathy were reported for 22 (18.8%) VIATORR Device and 24 (22.0%) Control Device subjects (p=0.621).

10.2.11. Thrombosis

Procedural thrombosis was reported in 16 VIATORR and 10 Control cases while post-procedural thrombosis occurred in 2 VIATORR and 9 Control cases. The majority of procedural thrombosis was in the splenic or portal vein, outside of the device, in 10 VIATORR and 8 Control cases.

10.2.12. Potential Adverse Events

Although not specifically reported during the pivotal clinical trial, the following are potential adverse events which may occur due to a TIPS procedure or the device:

- Vascular injury including
  - Rupture, Hematoma, or Pseudoaneurysm
  - Arteriovenous fistula
- Cerebrovascular accident
- Disseminated intravascular coagulopathy
- Pulmonary complications including
  - Embolism, pulmonary hypertension, ARDS
- Gall bladder or bile duct injury including hemobilia

10.3. Revision Cohort

De novo study subjects who required revision of their TIPS were eligible for enrollment into the subsidiary revision study. Subjects were required to have a > 50% DS in the *de novo* tract or a PSG > 12 mmHg. Revision was performed with a VIATORR device and subjects were followed out to 6 months (or outcome event). Subjects were assessed at 1 and 6 months for adverse events. Effectiveness was evaluated post-procedure by demonstrating a PSG $\leq$ 12 mmHg immediately following the procedure. Secondary endpoints included technical success and return of symptoms.

10.3.1. Subject Population

Twenty-eight (28) subjects were enrolled from the *de novo* study and the majority were from the Control arm (22/28, 78.6%). Most (18/28, 64.3%) required revision prior to the 6-month evaluation in the *de novo* study. Reasons for enrollment are shown in Table 20.

Table 20: Reasons for TIPS Revision

	Control Group	VIATORR Group
PSG > 12 mmHg alone	10	4
% DS > 50% alone	3	0
Abnormal PSG and % DS	9	1
Neither (protocol deviation)	0	1
TOTAL	22	6

10.3.2. Effectiveness Results

Four (4) subjects were not considered in the analysis as they entered the revision protocol with a baseline PSG < 12. Of the remaining 24 subjects, 20 (83.3%) were a hemodynamic success (PSG < 12 mmHg) following the procedure. In the entire study cohort (n=28), the mean PSG decreased from 18.3 mmHg to 8.9 mmHg, a 51%

reduction. The estimated probability of no return of symptoms through 6 months was 73.7% and at 30 days post-revision was 85.2%.

10.3.3. Safety Results

A total of 34 adverse events were reported during the 6 months following the revision procedure. Events which occurred in > 5% of subjects are summarized in Table 21.

Table 21: Reported Adverse Events

Adverse Event	Number of Subjects (%)
Ascites	5 (17.9%)
Encephalopathy	2 (7.1%)
Anemia	2 (7.1%)
Prosthesis Malposition	2 (7.1%)
Non-Variceal Bleeding	2 (7.1%)
Electrolyte Imbalance	2 (7.1%)
Bowel Other	2 (7.1%)

10.4. Training Cases

Each investigative site enrolled 2 VIATORR training cases as their first subjects under similar procedures as the larger *de novo* study above. Twenty (20) subjects underwent a *de novo* procedure and the remaining 8, a revision.

Results for Training Subjects Undergoing *de novo* TIPS (N=20)

Success as determined by primary patency at 6 months was as follows:

Success Rate

Intent-to-Treat (N=20)	40.0%
Modified ITT	(N=13) 61.5%
As Treated/Evaluable (N=9)	88.9%

Secondary effectiveness evaluations included the following:

Technical Success (N=20)	100%
Hemodynamic Success (N=19)	94.7%
Venographic Success (N=20)	90.0%
Mean Change in PSG	21.7 (N=20) to 9.2 mmHg (N=9)
%DS at 6 months (N=10)	12.9%

No reinterventions were required to maintain or re-establish patency in these subjects. A total of 33 adverse events were reported in 15 subjects. This included the following:

	Number of Events	Number of Subjects
Encephalopathy	8	7 (35%)
Ascites	4	4 (20%)
Anemia	3	3 (15%)
Hepatic Vein Stenosis	2	2 (10%)

Fever	2	2 (10%)

Results for Training Subjects Requiring TIPS Revision (N=8)

Only secondary effectiveness evaluations were performed for this group:

Technical Success (N=8)	100%
Hemodynamic Success (N=7)	100%
Mean change in PSG (N=3)	17.5 (N=8) to 8.3 mmHg (N=3)

A total of 4 adverse events were reported in 2 subjects including 2 cases of encephalopathy, both of which were considered serious.

11.0 Conclusions from the Studies

The data from the randomized controlled pivotal trial provides adequate assurance of the safety and effectiveness of the GORE VIATORR TIPS Endoprosthesis for the intended use.

The most common adverse event was hepatic encephalopathy (~40%) which is a known complication of creating a portosystemic shunt and was not unexpected or considered to be device-related. The only other events which occurred with a frequency of $\geq$ 10% in those subjects who received the VIATORR device was ascites (~20%) although this was actually an extension of the underlying disease rather than a new development in most cases. Events occurring at rates of 5-10% included anemia, hydrothorax, lower extremity edema, and renal dysfunction. The rates of adverse events (including serious events and death) with the use of the VIATORR device were consistent with or less than those seen with the Control device which is the only other TIPS stent currently available.

The results of the evaluation of patency consistently demonstrated effectiveness of the VIATORR device. Depending on the analysis, primary patency at 6 months was consistently better than for the control group (45-71% versus 22-39%). The VIATORR subjects had significantly fewer stenoses and reinterventions/revisions prior to the 6 month follow-up. In addition, secondary analyses revealed that the VIATORR group had a higher probability of remaining free of reintervention throughout the study and a longer time to initial reintervention. There were no statistically significant differences, however, in the probability of remaining free of symptoms or death.

Although the number of subjects evaluated for the use of the device in TIPS revision was significantly smaller and performed in a non-randomized or controlled manner, data from the revision study supported the safety of the device when used for such an indication. Although the rate of encephalopathy was lower (7.1% compared to approximately 40% in the *de novo* study), other adverse events were consistent with that seen in the *de novo* study. Immediate post-procedure hemodynamic success was achieved in 83.3% of subjects.

Overall, the comparative analysis of the clinical results for the test and control devices allows one to conclude that the benefits of use of the VIATORR Device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use. In conclusion, the data provided support both the safety and

effectiveness of the GORE VIATORR TIPS Endoprosthesis for the intended use proposed by the sponsor.

12.0 Panel Recommendation

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Cardiovascular Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

13.0 CDRH Decision

Expedited review status was granted on July 14, 2004 because FDA believed that the GORE VIATORR® TIPS Endoprosthesis may offer a viable alternative to the current standard of care for some patients with portal hypertension and its complications, which may be serious or life-threatening, or present a risk of serious morbidity. Because the device may address an unmet medical need by offering a significant, clinically meaningful advantage (a lined endoprosthesis versus a bare metal stent) and be in the best interest of patients.

FDA issued an approval order on December 6, 2004. The applicant's manufacturing facilities were inspected on July 27 – August 3, 2004, and August 16 – 20, 2004 and were found to be in compliance with the Quality System Regulation (21 CFR 820).

14.0 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.