

1 Review Summary

Panel Date: January 13, 2005
Lead Reviewers: Dorothy Abel, Biomedical Engineer
Matthew Krueger, Biomedical Engineer

Device: P040043
GORE TAG Thoracic Endoprosthesis
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Introduction

This report presents the FDA summary of the clinical, statistical, and pre-clinical testing review memorandums regarding P040043 for the GORE TAG Thoracic Endoprosthesis. The GORE device is a complete endovascular system consisting of the endovascular graft and the delivery system.

The FDA review team for this file is as follows:

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1.1 PMA Chronology

Information supporting the GORE TAG Thoracic Endoprosthesis was submitted as a modular PMA (M030017). The modular PMA process allows some sections of the PMA to be submitted early and reviewed by FDA prior to the submission of the pivotal clinical study results. If review of the modules is not completed prior to the submission of the clinical data, the modules are rolled into the PMA, as was the case for all of the modules submitted under M030017.

The following table provides a chronology of formal interactions for this PMA. Additional informal (e.g., e-mail, telephone) interactions, including requests for and receipt of clarification and information occurred throughout the review process and are not outlined here.

PMA CHRONOLOGY FOR P040043

Date	Event
09/30/04	Manufacturing module received
05/10/04	Biocompatibility module received
08/12/04	Non-clinical <i>in vivo</i> module received
12/17/04	Manufacturing module closed
09/20/04	Non-clinical <i>in vitro</i> module received
10/04/04	PMA received with clinical data to support the GORE TAG Thoracic Endoprosthesis
10/04/04	PMA filing date
1/13/05	Scheduled for review by Circulatory System Devices Panel

1.2 Executive Summary

The GORE TAG Thoracic Endoprosthesis is the first endovascular graft for treatment of thoracic aneurysms considered for marketing clearance by the FDA. Like most endovascular grafts, this device has been modified in response to clinical observations. Specifically, modifications were incorporated into the implant design of the GORE TAG Thoracic Endoprosthesis to minimize potential breaks (fractures) in the wire frame. Of note is that endovascular grafts for the treatment of abdominal aortic aneurysms have been approved for marketing despite observations of wire breaks, as the safety and effectiveness profile for these devices were determined to be favorable by the Circulatory System Devices Advisory Panel and the FDA.

The Gore TAG device first underwent clinical evaluation in the US in a feasibility study (██████████) followed by a pivotal study (██████████). After enrollment was completed for the pivotal study, wire fractures were identified in devices. These fractures have occurred in devices that have been implanted in patients for less than 3 months and up to 42 months. The majority of the fractures were of the longitudinal spine that was intended to provide longitudinal stiffness during the deployment of the device. The few other wire fractures were in the region where the wires were not bonded to the underlying graft material. Breaks were not associated with adverse events except for 8 cases worldwide of type III endoleaks caused by the fractured spine puncturing the graft material (5 type III endoleaks/39 devices with breaks/approximately 3000 devices distributed worldwide, 3 type III endoleaks/28 devices with breaks/approximately 600 patients in US studies).

Although the clinical results for the original design of the graft were favorable as compared to the surgical Control [e.g., the proportion of subjects who experienced \geq MAE through 1 year post-treatment was significantly lower ($p < 0.001$) in the TAG (42%) vs. Control (77%) group], the sponsor decided not to pursue marketing approval for the device until it could be redesigned to minimize the potential for wire fractures. The modifications to the device did not change the fundamental design of the implant; that is, both versions are constructed of an expanded polytetrafluoroethylene (ePTFE) tube reinforced with ePTFE/FEP (fluorinated ethylene propylene) film, with an external nitinol wire supporting structure bonded to the graft material with an ePTFE/FEP bonding tape.

The primary difference in the device designs is that the device evaluated in ██████████ and ██████████ had longitudinal spines, with unbonded portions of the wire structure to accommodate the spine. The modified device does not have longitudinal spines and the wire supporting structure is bonded in a uniform manner to the graft material. The graft material was also strengthened to provide the longitudinal stiffness previously provided by the spine. This graft material strengthening was accomplished by replacing several layers of the original reinforcing film with

layers of an additional stronger, less permeable ePTFE film. This results in an axially stiffer and less permeable graft material. This material is similar to the material incorporated into the commercially available EXCLUDER Bifurcated Endoprosthesis.

The device modifications eliminated the potential for spine fractures by removing the spine. The potential for other fractures was minimized by improving the attachment of the wire support to the graft material. To assess the influence of the device modifications on other performance characteristics, mechanical and preclinical in-vivo testing was performed. This testing addressed the potential for changes in the deployment accuracy, trackability through tortuous vessels, conformity to the vessel wall, foreshortening, migration resistance, elongation under pressure, strain in the device wire-frame, water entry pressure, bending durability and abrasion durability. The testing included a comparison to the original design. In all preclinical testing, the modified device performed as well or better than the original device, including long-term implant durability testing. To confirm the favorable results of the pre-clinical testing, a limited clinical study (b) (4) was conducted using the modified device design.

For all device modifications, whether implemented before or after marketing of the device, FDA considers the potential impact of the changes on device function when identifying the testing needed to verify that changes has not adversely affected device performance. For the GORE TAG Thoracic Endoprosthesis, this consisted of the pre-clinical testing and confirmatory clinical study. For the evaluation of this device, the clinical results from the original design are the primary dataset, with the pre-clinical and confirmatory clinical data from the modified device providing evidence to support approval of the current device design. Five-year data are reported for the feasibility study (b) (4), 24-month for the pivotal study (b) (4) and 30-day for the confirmatory study (b) (4).

1.3 Device Description

The GORE TAG Thoracic Endoprosthesis provides a means for endovascular repair of the descending thoracic aorta (DTA). This device is a flexible, self-expanding endoprosthesis that is constrained on the leading end of a delivery catheter. The system consists of two parts, the endoprosthesis and the delivery catheter. Sizes range in diameter from 26mm to 40mm and in length from 10cm to 20cm. The compressed profile of these devices on a delivery catheter ranges from 20-24Fr.

The endoprosthesis consists of an expanded polytetrafluoroethylene (ePTFE) tube reinforced with ePTFE/FEP (fluorinated ethylene propylene) film and an external nitinol wire supporting structure that is attached circumferentially along the entire surface of the graft with ePTFE/FEP bonding tape. A circumferential PTFE sealing cuff is located on the external surface of the endoprosthesis at the base of each flared end. Each cuff is circumferentially attached on one edge with FEP allowing the other edge to remain free to enhance sealing of the endoprosthesis to the wall of the aorta. In order to facilitate accurate endoprosthesis placement, two radiopaque gold bands are attached to the graft at the base of each flared end. A sleeve used to constrain the endoprosthesis on the leading end of the delivery catheter is made of ePTFE/FEP film. The sleeve is attached to the endoprosthesis with ePTFE fiber. The sleeve constrains the endoprosthesis and is sewn closed using an ePTFE deployment line, thereby constraining the endoprosthesis on the delivery catheter. The ePTFE sleeve remains *in situ* between the endoprosthesis and the vessel wall following deployment.

The delivery catheter has a multi-lumen shaft reinforced with a stainless steel mandrel. One catheter lumen is for 0.035" guidewire access and a separate lumen contains the ePTFE deployment line. Two tapered oval beads or "olives" are located on the delivery catheter at each end of the endoprosthesis to provide a smooth transition from the delivery catheter to the constrained endoprosthesis.

A two-arm adaptor is located on the proximal end of the delivery catheter. A Touhy-Borst valve is attached to the straight-arm and allows guidewire passage through the catheter. The Touhy-Borst valve also has a side flushing port that communicates with the guidewire lumen. A deployment knob is on the side-arm of the adaptor and is attached to the deployment line. To release the endoprosthesis, the deployment knob is turned and pulled, which removes the deployment line from the constrained endoprosthesis with unlacing initiating in the middle of the endoprosthesis and simultaneously extending toward both ends. This allows the endoprosthesis to self-expand rapidly.

1.4 Clinical

1.4.1 Alternative Practices and Procedures

Thoracic aortic aneurysms are a potentially lethal disease, and once rupture occurs, the fatality rate is >90%.¹ Descending thoracic aneurysms (DTA), a subset of aneurysms of the thoracic aorta, occur with an estimated frequency of 2.21 per 100,000 patient years with a fatality rate from rupture of 40%.²

Rupture of thoracic aneurysms is directly related to aneurysm size. In a natural history study of thoracic aneurysms, the average yearly rate of aneurysm rupture or dissection was <4% for aneurysms 5.0 to 5.9 cm in diameter and increased to 6.9% for aneurysms ≥ 6.0 cm in diameter; the yearly rate of rupture, dissection, or death was 15.6% for aneurysms ≥ 6.0 cm.³ Most patients with thoracic aneurysm have concurrent medical conditions that increase their risk for major surgery including hypertension, COPD, heart failure, peripheral and cerebrovascular disease, and abdominal aortic aneurysm.⁴

The standard treatment for patients with DTA aneurysm involves thoracotomy with surgical resection of the diseased aorta and replacement with prosthetic graft material. However, open surgical repair is associated with substantial in-hospital mortality; operative mortality for elective surgery ranges from 3 to 20% and is over 50% in emergency cases.⁵⁻⁹ Further, major morbidity is associated with open surgical repair. A paraplegia rate of 18% has been reported for surgical repair of thoracic aortic aneurysms.¹⁰ Other important post-operative complications include bleeding, stroke, renal insufficiency, and respiratory failure.¹¹

1. Estrera AL, et al. Descending thoracic aortic aneurysm: surgical approach and treatment using the adjuncts cerebrospinal fluid drainage and distal aortic perfusion. *Ann Thorac Surg* 2001;72: 481-6.

2. Coselli JS, et al. Thoracoabdominal aorta. *Cardiol Clin* 1999; 17: 751-65.

3. Davies RR, et al. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg* 2002; 73: 17-28.

4. Bickerstaff LK, et al. Thoracic aortic aneurysms: a population based study. *Surgery* 1982; 92: 1103-8.

5. Galloway AC, et al. Selective approach to descending thoracic aortic aneurysm repair: a ten-year experience. *Ann Thorac Surg* 1996; 62: 1152-7.

6. Biglioli P, et al. Quick, simple clamping technique in descending thoracic aortic aneurysm repair. *Ann Thorac Surg* 1999; 67: 1038-43.

7. Najibi S, et al. Endoluminal versus open treatment of descending thoracic aortic aneurysms. *J Vasc Surg* 2002; 36: 732-7.

8. Lepore V, et al. Treatment of descending thoracic aneurysms by endovascular stent grafting. *J Card Surg* 2003; 18: 436-43.

9. Czerny M, et al. Stent-graft placement in atherosclerotic descending thoracic aortic aneurysms: midterm results. *J Endovasc Ther* 2004; 11: 26-32.

10. Johnston KW, et al. Suggested standards for reporting on arterial aneurysms. Subcommittee on Reporting Standards for Arteria Aneurysms, Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery and North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg 1991; 13: 452-8.
11. Deeb GM, et al. Retrograde cerebral perfusion during hypothermic circulatory arrest reduces neurologic morbidity. J Thorac Cardiovasc Surg.1995; 109:259-68.

1.4.2 Clinical Studies

Endovascular placement of endovascular grafts is a less invasive method of treating DTA aneurysms as compared to surgical repair. However, there are risks unique to endovascular repair including endoprosthesis material failure, endoleak, endoprosthesis migration, branch vessel occlusion, vascular complications related to device entry and deployment failure. Endovascular repair also requires regular radiologic observation to monitor the endoprosthesis and adjacent aorta. In order to determine the risk/benefit profile of the GORE TAG Thoracic Endoprosthesis, clinical studies were conducted.

Table 1 summarizes the clinical studies for the GORE TAG Thoracic Endoprosthesis.

Table 1: Summary of studies with original and current device designs

Title	Device	Enrollment Period	Number of Patients Enrolled	Number of Sites
Feasibility (██████████)	Original design	2/98-2/99	28	2
Pivotal (██████████)	Original design	9/99-5/01 TAG 11/93-9/99 Historical 9/99-5/01 Concurrent*	TAG - 140 Control - 94	17 15
Confirmatory (██████████)	Current design	1/2004-6/-04	51	11
Emergency Use/Compassionate Use	Original design	3/98-5/01	66	27
	Current design	N/A	None	N/A
SI studies	Original design	2/00-7/04	196	3
	Current design	12/03-ongoing	99	3
Treatment IDE (██████████)	Current design	8/04 - ongoing	36	11
High Risk Protocol (██████████)	Current Design	Awaiting IRB approval	0	15
Total	Original design	2/98-7/04	430	36
	Current design	12/03-ongoing	186	12

*the majority of Control patients were treated from January 1998 to May 2001

The Feasibility Study provided the initial clinical experience with the device, and the results were used in the justification and design of the Pivotal Study protocol. In addition, patients in the Feasibility Study have been followed out to 5 years providing important data on the durability of this treatment.

In the Pivotal Study, it is notable that a relatively large number of patients (n=140) were treated, given the incidence of thoracic aneurysms. The Pivotal Study demonstrated that the device could be successfully deployed and was associated with a reduced rate of major adverse events though 1 year (primary safety endpoint). Follow-up data show that this reduction of adverse events was maintained to least 2 years. The absence of ruptures and the minimal device related events (through 2 years) reflect favorably on the risk/benefit profile for this device. These results serve as the foundation for the evaluation of the current version of the device.

While not associated with adverse events in the Pivotal Study, spine wire fractures were recognized in a small number of patients. In response, the Sponsor elected to modify the device. Based on pre-clinical evaluations, the device modifications were not expected to adversely affect the device performance; however, since the changes could potentially affect the deployment

reliability, the Confirmatory Study was conducted. A 30-day endpoint was chosen for the Confirmatory Study as the majority of device-related events (75%), and all aneurysm related deaths, for device-treated patients in the Pivotal Study were observed within 30 days post-procedure. Results from this Confirmatory Study confirmed that the device modifications did not adversely affect clinical outcomes.

Continued clinical follow-up is necessary to provide comprehensive long-term information about the risks and benefits of this device when used for the treatment of descending thoracic aneurysms. These data should be provided in yearly clinical updates to physician users, post-device approval.

1.4.2.1 Feasibility Study (██████████)

The Feasibility Study was conducted at 2 investigational sites and included the enrollment of 28 patients (19 men, 9 women, mean age 66±13 years) requiring treatment of DTA aneurysms. The original device design was used in this study. The purpose of the study was to establish preliminary device safety. Safety and efficacy variables of interest and inclusion/exclusion criteria were generally similar to those for the TAG subjects in the Pivotal Study (see 1.1.4.2).

Safety: Death within 30 days post-treatment was 3.6%, and through 1 year was 21% (estimated 60-month mortality 36%). The incidence of subjects experiencing ≥ adverse event was 57% through 1 year; however, paraplegia (0%), stroke, (0%), renal failure (3.6%) and myocardial infarction (3.6%) were rarely observed.

Efficacy: There were no endoprosthesis deployment failures observed. Two endoleaks occurred in the first 30 days post-treatment, both of which resolved without treatment. Through 60 months post-treatment, there were no aneurysm ruptures, endoprosthesis migration, extrusion/erosion, lumen obstruction, branch vessel occlusion, or endoprosthesis realignment. Endoprosthesis fractures were noted in 9 subjects (32%); however, no fractures were associated with clinical sequelae.

Endoleaks were observed in 6 subjects (21%), 2 of who required intervention (1 revision, 1 conversion). Aneurysm enlargement was observed in 5 subjects (18%) through the 60-month follow-up period, 1 of whom required reintervention.

1.4.2.2 Pivotal Study (TAG 99-01)

Clinical Study Design

The pivotal study for the GORE TAG Thoracic Endoprosthesis in the treatment of DTA aneurysms was a non-blinded, non-randomized, controlled study referred to as ██████████. The safety objective of ██████████ was to compare the safety of endovascular repair with the original design of the GORE TAG Thoracic Endoprosthesis to a surgical repair control group. The Control group was comprised of recently treated retrospectively enrolled open surgical repair patients (n=50) and concurrently enrolled open surgical repair patients (n=44). The efficacy endpoint of ██████████ was to assess the effectiveness of the GORE TAG Thoracic Endoprosthesis in the treatment of DTA aneurysms.

This was a multicenter study that enrolled 234 patients from 17 clinical sites in the US who required treatment of DTA and who met the study eligibility criteria (see below). No investigational site treated more than 13% of the TAG subjects.

Control Group

The Control group consisted of two groups of patients: 1) a historical control group (n=50); and 2) a concurrent control group (n=44). The historic control group consisted of patient who had recently undergone open surgical repair of a DTA aneurysm at participating centers. This group was filled by enrolling patients with the most recent procedure and working sequentially backward, with treatment dates from November 1993 to September 1999. The concurrent surgical control group consisted of subjects who failed screening for the TAG device (e.g., inadequate neck length or unsuitable neck diameters) and were scheduled to undergo open surgical repair. These latter patients were treated from September 1999 to May 2001. There was to be no more than a 5 subject enrollment difference between TAG and Control subjects at each study site.

Eighty-two percent of the surgical Controls had their procedures between January 1998 and May 2001. The historical and concurrent control groups were similar with respect to major demographic variables and clinical variables.

Subject Follow-up

Subjects were evaluated for adverse events and device-related events that occurred through hospital discharge. Follow-up visits were completed at 30 days and 6 months post-treatment and annually thereafter (to continue through 5 years). A 3-month follow-up evaluation was scheduled if an endoleak was identified at 30 days post-treatment. TAG subjects underwent a CXR at 6, 12, and 24 months. A CT scan was performed in TAG subjects at 1, 6, 12, and 24 months.

Study Endpoints

Safety: The primary safety endpoint was the proportion of subjects who experienced \geq major adverse event (MAE) through 1 year post-treatment. Comparisons were made between subjects treated with the GORE TAG Thoracic Endoprosthesis (TAG) and open surgical repair (Control).

The safety null hypothesis was that the proportion of subjects who experienced \geq major adverse event (MAE) through 1 year post-treatment was equal in the Control subjects and the TAG subjects. The alternate hypothesis was that the proportion of subjects who experienced \geq major adverse event (MAE) through 1 year post-treatment was less in the TAG subjects than in the Control subjects. The primary safety endpoint is a composite outcome consisting of the occurrence within 1 year post-procedure of any of the following MAEs:

- bleeding (procedural and post-procedural)
- coagulopathy
- hematoma
- atelectasis/pneumonia
- pulmonary embolism
- respiratory failure
- angina
- arrhythmia
- CHF
- MI
- renal failure
- renal insufficiency
- lymphocele/lymph fistula
- wound infection
- ileus
- bowel ischemia
- bowel obstruction
- amputation
- AV fistula
- embolism
- pseudoaneurysm
- restenosis
- thrombosis
- vascular trauma
- nerve injury
- paraplegia/paraparesis
- spinal neurological deficit
- TIA
- anatomic false aneurysm
- aortoenteric fistula
- erectile dysfunction
- prosthesis dilatation/rupture
- post-implant syndrome
- prosthetic infection

- wound dehiscence
- leg edema
- CVA
- mental status change
- femoral neuropathy
- prosthetic thrombosis
- reoperation
- death

Adverse events were categorized by severity, as follows:

Major

- Require therapy, minor hospitalization (< 48 hours)
- Require major therapy, unplanned increase in level of care, prolonged hospitalization (> 48 hours)
- Permanent adverse sequelae
- Death

Minor

- No therapy, no consequence
- Nominal therapy, no consequence; includes overnight admission for observation only

Efficacy: The primary efficacy endpoint was the proportion of subjects treated with the GORE TAG Thoracic Endoprosthesis who were free from a major device-related event through the 12-month follow-up visit. Device-related events in the TAG group were only evaluated descriptively and were not compared to the Control group.

The efficacy null hypothesis was that the proportion of subjects treated with the TAG device free from a major device-related event through the 12-month follow-up visit would be ≤ 0.8 . The alternate hypothesis was that the proportion of subjects treated with the TAG device free from a major device-related event through the 12-month follow-up visit would be > 0.8 . This endpoint was a composite outcome consisting of subjects who were free from the following major device-related events: aneurysm enlargement, endoleaks, aneurysm rupture, branch vessel occlusion, deployment failure, extrusion/erosion, lumen obstruction, prosthesis material failure, prosthesis migration, and prosthesis realignment.

When formalizing the efficacy hypotheses, the efficacy of open surgical repair was assumed to be 100%. A point estimate of 80% was judged to be a reasonable efficacy outcome for the endovascular treatment. The Agency and the sponsor agreed to an analysis plan where the device would need to show superior safety as the efficacy was expected to be less than that for surgical repair.

Secondary Outcomes: The secondary outcomes included procedural blood loss, length of intensive care unit and hospital stay, and the time to return to normal daily activities. Comparisons were made between subjects treated with the GORE TAG Thoracic Endoprosthesis and open surgical repair Controls.

The null hypothesis was that the Control group blood loss, length of stay, and return to normal activities was less than or equal to those for the TAG group. The alternate hypothesis was that the Control group blood loss, length of stay, and return to normal activities was greater than those for the TAG group.

Key Inclusion/Exclusion Criteria

Control Group Inclusion Criteria

- DTA aneurysm deemed to warrant surgical repair (fusiform aneurysm ≥ 2 times diameter or normal adjacent aorta or saccular aneurysm)

- Surgical DTA aneurysm repair using surgical clamps places placed distal to the left carotid artery and proximal to the celiac artery
- Surgical candidate
- Age ≥ 1

Control Group Exclusion Criteria

- Mycotic aneurysm
- Hemodynamically unstable aneurysm
- Aortic dissection (acute or chronic)
- Other planned surgical procedure
- MI or CVA within 6 weeks
- Creatinine >2.0 mg/dl
- Connective tissue disease

TAG Group Inclusion Criteria

- DTA aneurysm deemed to warrant surgical repair (fusiform aneurysm ≥ 2 times diameter or normal adjacent aorta or saccular aneurysm)
- Anatomy meets EXCLUDER specification criteria (a) aortic inner diameter 23-37 mm, (b) lack of significant thrombus and/or calcification in the proximal or distal aortic implantation sites, and (c) Minimum 2 cm non-aneurysmal segment proximal and distal to the aneurysm
- Surgical candidate
- Age ≥ 1

TAG Group Exclusion Criteria

- >4 mm aortic taper and inability to use devices or different diameters to compensate for the taper
- Thrombus at the proximal or distal implantation sites
- Mycotic aneurysm
- Hemodynamically unstable aneurysm
- Aortic dissection (acute or chronic)
- Other planned surgical procedure
- MI or CVA within 6 weeks
- Severe respiratory insufficiency (which would preclude an open procedure)
- Creatinine >2.0 mg/dl
- Connective tissue disease
- History of drug abuse with 6 months

Sample Size and Statistical Considerations

For the safety hypothesis, the null hypothesis was that the complication rate for the Control group would be \leq the complication rate for the TAG group. It was assumed that the complication rate for the Control group would be 40% vs. 20% in the TAG group. A 2-sided test with an alpha of 0.05 and a power of 80% were used. A sample size of 82 evaluable patients in each treatment group was projected (maximum 236 subjects; 96 Control patients and 140 TAG patients). Primary endpoints were analyzed on an intent-to-treat basis. The primary endpoint and the incidence of acute and late complications were tested using chi-square analysis. Exclusion of the DTA aneurysm from the circulating blood was to be calculated by the life-table method or Kaplan Meier plots. The influence of pertinent comorbidities was to be analyzed using Cox regression analysis.

Study Results

Patients: There were 140 patients (71±10 years old, 57% male) treated with the original design of the GORE TAG Thoracic Endoprosthesis and 94 historical surgical Controls (68±10 years old, 51% male). Baseline demographic and clinical characteristics were similar between the treatment groups. Risk factors commonly reported as moderate or severe were hypertension (48% TAG, 46% Control), hyperlipidemia (36% TAG, 25% Control), and tobacco use (28% TAG, 21% Control). The majority of TAG (89%) and Control (92%) subjects were classified by the American Society of Anesthesiologists (ASA) as class III or IV.

There was a different distribution of NYHA classification between the groups (NYHA class II - 43% TAG, 29% Control; NYHA class III - 9% TAG, 25% Control), as well as a higher prevalence of symptomatic aneurysm in the Control group (21% TAG, 38% Control). With regard to the NYHA class, the high frequency of missing data (42% of TAG patients and 49% of Controls) calls into question the validity of any statistical analysis. The clinical relevance of the difference in the prevalence of symptomatic aneurysms warrants panel discussion.

DTA Aneurysm Assessment: Pre-treatment aneurysm diameter was similar between the TAG (64 ± 15 mm) and Control (63 ± 16 mm) groups. Aortic diameter was smaller in the TAG group proximal (31 ± 4 vs. 34 ± 8 mm) and distal (30 ± 4 vs. 34 ± 7 mm) to the aneurysm. Proximal (63 ± 39 vs. 58 ± 56 mm) and distal (80 ± 55 vs. 70 ± 52 mm) aortic neck lengths were longer in the TAG group. However, missing data in the Control group precluded statistical analyses of these latter variables.

Devices Implanted: During the initial procedure, 234 endoprostheses were implanted in 137 TAG Subjects. The vast majority received 1 (61, 45%) or 2 (60, 44%) devices. No subject required more than four endoprostheses. An endoprosthesis was not implanted in 3 (2.1%) subjects due to access failure. A plurality (102, 44%) of implanted endoprostheses were 34 mm in diameter, while 41 (18%) were 37 mm, 41 (18%) were 40 mm, and 32 (14%) were 31 mm. The 26 and 28 mm diameter endoprostheses were rarely implanted (9, 3.8% each). The distribution of the lengths of the implanted endoprostheses was 15 mm (76, 32%), 10 mm (70, 30%), 20 mm (54, 23%), 12.5 mm (32, 14%), and 7.5 mm (2, 1%).

Outcomes:

Safety: The proportion of subjects who experienced \geq MAE through 1 year post-treatment was significantly lower ($p < 0.001$) in the TAG (42%) vs. Control (77%) group. Ten (7.1%) TAG subjects had no 12-month follow-up visit. Assuming that all 10 TAG subjects experienced a MAE through 1 year post-treatment, the estimated 1-year MAE incidence in the TAG group increased from the 42% to 49%. However, the significance level for the comparison with the Control group remained < 0.001 .

Notably, the rate of neurological complications for the TAG group was 11% vs. 33% for the Control group. Of these neurological complications, 3% of TAG vs. 14% of Controls had paraplegia/paraparesis/spinal neurological deficit.

The incidence of the following individual MAE was lower in TAG subjects vs. Controls, respectively, through 1 year post-treatment: major bleeding [11% vs. 54% (41% procedural)], pulmonary [13% vs. 38% (23% respiratory failure)], renal [4% vs. 15% (10% renal insufficiency)], and wound [6% vs. 15% (12% infection)]. TAG subjects experienced more major vascular complications than Control subjects [18% (11% vascular trauma) vs. 6%].

The all-cause mortality through 1 year post-treatment was 21% for the Control vs. 17% for TAG subjects; however, aneurysm-related mortality was lower in TAG subjects (3%) vs. Control subjects (10%) through 1 year post-treatment. The incidence of cardiac complications was lower in TAG subjects at 30 days, but became similar to Controls by 1 and 2 years. Five percent of TAG patients and 7% of Controls had CVA's. There were no differences between TAG and Control subjects in the rates of bowel complications.

Table 2 provides values for the more salient observations from this study. The complete table of MAEs can be found in the major adverse events section of the [REDACTED] pivotal study summary, Table 15 (Primary safety endpoint: major adverse events through 365 days post-treatment), pages 52-53 of the panel package. Study mortality is addressed in a separate section of this memorandum.

Table 2: Safety - MAEs through 365 days post-treatment

Safety endpoints	TAG (n=140) n (%)	Control (n=94) n (%)	Estimated risk difference* (95% CI)
Any major adverse event	59 (42)	72 (77)	34 (21.72, 47.18)
Bleeding complications	16 (11)	51 (54)	43 (30.57, 55.08)
Coagulopathy	1 (1)	9 (10)	
Procedural	7 (5)	39 (41)	
Post-procedural	4 (3)	13 (14)	
Pulmonary complications	18 (13)	36 (38)	25 (13.27, 37.61)
Atelectasis / pneumonia	13 (9)	20 (21)	
Respiratory failure	11 (8)	22 (23)	
Cardiac complications	22 (16)	22 (23)	8 (-3.67, 19.05)
Arrhythmia	12 (9)	18 (19)	
Myocardial infarction	7 (5)	2 (2)	
Renal function complications	6 (4)	14 (15)	11 (1.78, 19.44)
Renal failure	3 (2)	7 (7)	
Renal insufficiency	3 (2)	9 (10)	
Wound complications	9 (6)	14 (15)	8 (-0.69, 17.62)
Wound infection	5 (4)	11 (12)	
Vascular complications	25 (18)	6 (6)	-11 (-20.40, -2.54)
Thrombosis	8 (6)	4 (4)	
Vascular trauma	15 (11)	0	
Neurologic complications	15 (11)	31 (33)	22 (10.58, 33.95)
Cerebrovascular accident	7 (5)	7 (7)	
Paraplegia paraparesis/spinal neurological deficit	4 (3)	13 (14)	

*p-values are not shown because no a priori adjustment for multiple hypothesis testing was performed. However, please note that an unadjusted risk difference that does not cross zero corresponds to a p-value of <0.05

Six (4%) TAG subjects required implantation of an additional endoprosthesis to treat the aneurysm through 1 year post-treatment (Table 3). No Control patients underwent reoperation.

Table 3: Reasons for implantation of additional endoprosthesis

Reason for Intervention	Number of Patients
Deployment Failure	1
Endoleak	1
Aneurysm Enlargement	1
Endoleak and Aneurysm Enlargement	2
Endoleak, Aneurysm Enlargement and Prosthesis Migration	1
Total	6

Major adverse events as a function of follow-up duration. The complete table of MAEs by follow-up period can be found at the end of the major adverse events section of the [REDACTED] pivotal study summary, Table 20 (Additional safety evaluations: major adverse event by follow-up period), pages 60-61 of the panel package. During the first 30 days post-treatment, 40 (29%) TAG subjects and 66 (70%) Control subjects reported ≥ 1 MAE, reflecting the differences in safety as described above for the 1-year evaluation. During the period 31-365 days post-treatment, 37 (28%) TAG and 22 (26%) Control subjects reported the occurrence of an MAE. No between-group differences were observed in any MAE subgroup. During the period 366-730 days post-treatment, 15 (14%) TAG and 6 (9%) Control subjects reported the occurrence of at least one MAE. The incidence of MAEs was clustered in the first 30 days.

Results through 2 years post-treatment. The proportion of subjects who experienced ≥ 1 MAE through 2 years post-treatment was lower in the TAG (49%) vs. Control (78%) group. The incidence of major bleeding (13% vs. 54%), pulmonary (16% vs. 38%), renal (5% vs. 15%), wound (7% vs. 16%), and neurologic (13% vs. 34%) complications was lower in the TAG group. No between-group differences were noted in the incidence of major cardiac, bowel, or other. The TAG group experienced more major vascular complications than the Control group (18% vs. 6%). No additional TAG patients required reoperation to treat the aneurysm through 2 years post-treatment.

Kaplan-Meier estimates through 2 years post-treatment showed a lower proportion of subjects treated with the GORE TAG Thoracic Endoprosthesis experienced ≥ 1 MAE compared to open surgical repair Controls (Figure 1, Table 4). A relative reduction of MAE incidence of 61% was noted after 14 days post-treatment in the TAG group and remained at 37% through 2 years post-treatment.

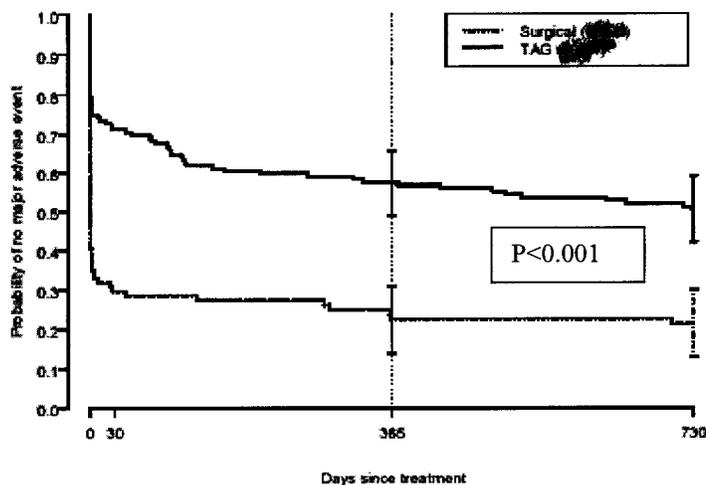


Figure 1: Subjects free of a major adverse event through 2 years post-treatment

Table 4: Subjects free of a major adverse event through 2 years post-treatment

Days from treatment	TAG Device (N=140)			Surgical Control (N=94)			Probability of remaining event-free from Day 0	
	Number event-free at start of interval	Number with event	Number censored	Number event-free at start of interval	Number with event	Number censored	TAG device	Surgical Control
[0, 30]	140	40	2	94	66	1	0.71	0.30
(30, 182]	98	15	0	27	2	1	0.60	0.27
(182, 365]	83	4	3	24	4	1	0.57	0.23
(365, 730]	76	9	10	19	1	3	0.50	0.21

¹ (lower endpoint, upper endpoint] denotes > lower endpoint and <= upper endpoint.

² Subjects who withdrew are considered censored.

Note: Column header are the number of subjects enrolled. Probability of remaining event-free is the Kaplan-Meier estimate.

Deaths. Total mortality and the causes of death were classified by the investigative sites and reviewed by the CEC. No between-group difference was noted in all-cause mortality through 2 years post-treatment [24% TAG (n=34), 26% Control (n=24)]. While an early advantage was observed in the TAG group, the Kaplan-Meier estimate and log-rank statistic of the survival probabilities confirmed that there was no difference in mortality between the TAG and Control group through 2 years post-treatment (Figure 2, Table 5). Aneurysm related mortality was defined as death due to rupture, death prior to 30 days or hospital discharge from the primary procedure, or death less than 30 days from a secondary procedure designed to treat the original aneurysm. Aneurysm-related mortality was lower in the TAG (3%) vs. Control (10%) groups through 2 years post-treatment (Figure 3, Table 6). No device-related deaths were noted through 2 years post-treatment.

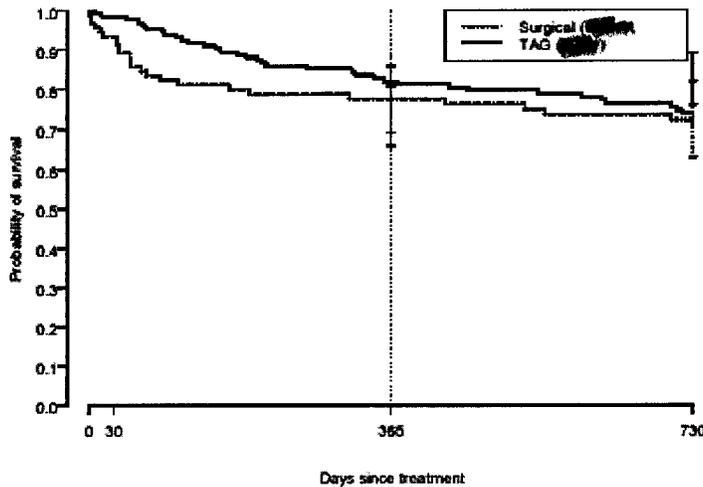


Figure 2: All-cause mortality through 2 years post-treatment

Table 5: All-cause mortality through 2 years post-treatment

Days from treatment	TAG Device (N=140)			Surgical Control (N=94)			Probability of remaining alive from Day 0	
	Number alive at start of interval	Number died	Number censored	Number alive at start of interval	Number died	Number censored	TAG Device	Surgical Control
[0, 30]	140	2	4	94	6	3	0.99	0.94
[30, 182]	134	13	1	85	12	7	0.89	0.80
[182, 365]	120	9	6	66	2	2	0.82	0.78
[365, 730]	105	10	16	62	4	9	0.74	0.72

¹ (lower endpoint, upper endpoint] denotes > lower endpoint and <= upper endpoint.

Note: Column header are the number of subjects enrolled. Probability of remaining alive is the Kaplan-Meier estimate.

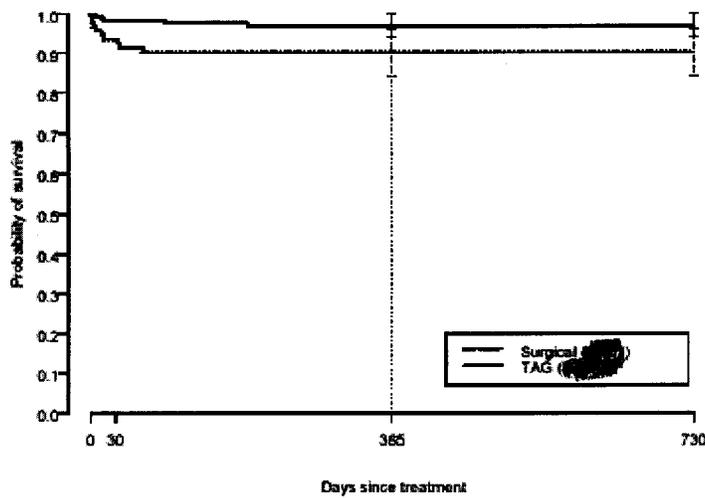


Figure 3: Aneurysm-related mortality through 2 years post-treatment

Table 6: Aneurysm-related mortality through 2 years post-treatment

Days from treatment	TAG Device (N=140)			Surgical Control (N=94)			Probability of remaining alive from Day 0	
	Number alive at start of interval	Number died	Number censored	Number alive at start of interval	Number died	Number censored	TAG Device	Surgical Control
[0, 30]	140	2	4	94	6	3	0.99	0.94
(30, 182]	134	1	13	85	3	16	0.98	0.90
(182, 365]	120	1	14	66	0	4	0.97	0.90
(365, 730]	105	0	26	62	0	13	0.97	0.90

¹ (lower endpoint, upper endpoint] denotes > lower endpoint and <= upper endpoint.

Note: Column headers are the number of subjects enrolled. Probability of remaining alive is the Kaplan-Meier estimate.

Minor adverse events. The proportion of subjects who experienced \geq minor AE through 1 and 2 years post-treatment was lower in the TAG (49% and 51%) vs. Control (60% and 61%) group, respectively.

Efficacy: The freedom from a major device-related event for the TAG device was 87 to 94 percent. Eight (6%) subjects experienced \geq major device-related event through the 12-month follow-up visit. The efficacy null hypothesis was that the proportion of subjects free from a major device-related event through the 12-month follow-up visit would be < 0.8 . The TAG efficacy estimate was 0.94 with a lower bound 95% confidence interval of 0.90, and the null hypothesis was rejected ($p < 0.0001$) in favor of the alternate hypothesis that the probability was ≥ 0.8 . These calculations assume that the 10 TAG subjects without a 12-month follow-up visit had no major device-related events. If one assumes that all 10 subjects without a 12-month follow-up visit had a major device-related event in this period, the estimate of the probability of not having a major device-related event was 0.87, and the null hypothesis was still rejected ($p = 0.02$, 1-sided).

Table 7 provides values for the more salient efficacy observations from this study. The complete table of efficacy endpoints can be found in the primary efficacy outcome section of the TAG pivotal study summary, Table 25 (Efficacy endpoint: major device-related events through the 12 month follow-up visit), page 69 in the panel package.

Table 7: Efficacy – Major device-related events through 12 month follow-up visit

Major device-related event	TAG (N = 140), n (%)	95% confidence interval
Any major device-related event	8 (6)	(1.51, 9.92)
Endoleak	4 (3)	(0.00, 5.97)
Type I	3 (2)	
Ia (proximal)	3 (2)	
Ib (distal)	0	
Type II	0	
Type III	0	
Type IV	0	
Indeterminate	1 (1)	
Aneurysm rupture	0	
Treatment-related device event	2 (1)	(0.00, 3.75)
Access failure	0	
Deployment failure	1 (1)	
Other device complication at treatment	1 (1)	
Unplanned occlusion of a branch vessel	1 (1)	(0.00, 2.47)
Celiac axis	1 (1)	
Renal	1 (1)	
Superior mesenteric	1 (1)	
Lumen obstruction	0	
Prosthesis migration	1 (1)	(0.00, 2.47)
Prosthesis realignment	0	
Prosthesis material failure	0	
Aneurysm enlargement	3 (2)	(0.00, 4.90)

The influence of baseline variables on the risk of a TAG subject experiencing a major device-related event was assessed with univariate logistic regression analyses. Of the 40 variables evaluated, 3 were independently related to an increased risk of a device-related event: 1) Caucasian race; 2) a larger aortic diameter immediately proximal to the aneurysm; and 3) a larger aneurysm diameter.

Major efficacy outcomes as a function of follow-up duration. Eight (8) patients had at least one major device related event, with a total of 11 events. No aneurysm ruptures were observed through 2 years post-treatment in the TAG group. There were 4 reports of major endoleaks (3

proximal Type I and 1 indeterminate) and 3 reports of aneurysm enlargement (\geq mm increase in aneurysm diameter from the 1 month visit) that required treatment through 12 months. Through 2 years post-treatment, 97% of TAG subjects remained free of an endoleak that required intervention. The proportion of TAG subjects that showed no change or a decrease in aneurysm diameter was 92% through 6 months (n=83 patients with complete data), 90% (n=83 patients) through 12 months, and 87% (n=67 patients) through 24 months post-treatment. Of the 8 subjects with a major device-related event reported through the 12-month follow-up visit, 6 (75%) had their event within 1-month of their procedure.

Endoleaks. Endoleaks were categorized as major and minor based on severity, consistent with the assessment of all adverse events, and are reported in Table 8.

Table 8: Endoleaks by follow-up periods

	Through Month 1 visit		Post-treatment follow-up period Month 1 visit to Month 12 visit (N=123)		Month 12 visit to Month 24 visit (N=100)	
	Minor (%)	Major (%)	Minor (%)	Major (%)	Minor (%)	Major (%)
Endoleak	19 (14)	3 (2)	1 (1)	1 (1)	2 (2)	0
Type I	11 (8)	2 (1)	1 (1)	1 (1)	0	0
Ia	10 (7)	2 (1)	1 (1)	1 (1)	0	0
Ib	2 (1)	0	0	0	0	0
Type II	3 (2)	0	0	0	1 (1)	0
Type III	3 (2)	0	0	0	1 (1)	0
Type IV	0	0	0	0	0	0
Indeterminate	3 (2)	1 (1)	0	0	0	0

Secondary Outcomes: The TAG group had shorter median intensive care unit (1 vs. 3 days, $p < 0.001$) and hospital (3 vs. 10 days, $p < 0.001$) stays. The evaluation of procedural blood loss and time to return to normal daily activity was compromised by a high proportion of missing data; descriptive data (without hypothesis testing) show that the TAG group experienced less median blood loss (250 vs. 1850 ml) and returned to normal daily activities sooner (30 vs. 78 days) as compared to Controls.

Wire Fractures: The imaging core laboratory observed 19 prosthesis material failures (all wire fractures) through the 24-month follow-up visit; 1 was reported through the 1-month follow-up visit, 6 between the 1- and 12-month visits, and 12 between the 12- and 24-month visits. To date, the only adverse events associated with breaks in the spine are type III endoleaks (8 cases worldwide).

Protocol Deviations: Five (5) protocol deviations, all of which were exclusion criteria violations, occurred in 5 (3.6%) TAG subjects during the study. Deviations consisted of inclusion of patients with renal insufficiency (2), presence of aortic dissection (1), recruitment of a nonsurgical candidate (1), and subclavian bypass performed at time of endovascular treatment (1). Eleven (11) protocol deviations were observed in 11 (11.7%) Control subjects during the study. These deviations included six informed consent issues, three inclusion and two exclusion criteria violations.

Extended Follow-up: Patient follow-up is ongoing and will continue through 5 years post-treatment. Three-year data from the [REDACTED] Study will be submitted in the IDE annual report in February 2005.

1.4.2.3 Confirmatory Study (TAG 03-03)

Clinical Study Design

The confirmatory study for the GORE TAG Thoracic Endoprosthesis in the treatment of DTA aneurysms was a non-blinded, non-randomized, prospective, single-arm study referred to as TAG [REDACTED]. The objective of [REDACTED] was to support the results of the preclinical testing used to compare the performance of the current device and the original device designs.

This was a multicenter study that enrolled 51 patients from 11 clinical sites who required treatment of DTA and who met the study eligibility criteria. All except one of the clinical sites also participated in the pivotal study ([REDACTED]). To support the comparability of the data between studies, [REDACTED] and [REDACTED] used the same Inclusion/Exclusion criteria, screening assessments, CEC and Core laboratory. In addition, both studies collected identical study data (e.g., adverse events, device events).

Control

The surgical Control subjects enrolled in [REDACTED] served as a Control group for the confirmatory study. The [REDACTED] TAG group was also used for comparison.

Subject Follow-up

Subjects were evaluated for adverse events and device-related events that occurred through hospital discharge. Follow-up visits were completed at 30 days post-treatment and annually thereafter (to continue through 5 years) and included CXR and CT scans. A 3-month follow-up evaluation was scheduled if an endoleak was identified at 30 days post-treatment.

Study Endpoints

Safety: The primary safety endpoint was the proportion of subjects who experienced \geq major adverse event (MAE) through 30 days post-treatment. Comparisons were made between subjects treated with the GORE TAG Thoracic Endoprosthesis (TAG) and open surgical repair (Control).

The safety null hypothesis was that the proportion of subjects who experienced \geq major adverse event (MAE) through 30 days post-treatment was equal in the Control subjects and the TAG subjects. The alternate hypothesis was that the proportion of subjects who experienced \geq major adverse event (MAE) through 30 days post-treatment was less in the TAG subjects than in the Control subjects. The primary safety endpoint is a composite outcome consisting of the occurrence within 30 days post-procedure of any of the MAEs as defined in [REDACTED] and listed above.

Efficacy: The primary efficacy endpoint was the proportion of subjects treated with the GORE TAG Thoracic Endoprosthesis who were free from a major device-related event through the 30 day follow-up visit. Device-related events in the TAG group are presented descriptively.

Secondary Outcomes: The secondary outcomes included procedural blood loss, length of intensive care unit and hospital stay, and the time to return to normal daily activities. Comparisons were made between subjects treated with the GORE TAG Thoracic Endoprosthesis and open surgical repair Controls.

Sample Size and Statistical Considerations

Sample size calculations were based on the primary safety hypothesis, and a comparison of the proportion of subjects with ≥ 1 MAE between the TAG and Control subjects enrolled in TAG. For the safety hypothesis, the null hypothesis was that the complication rate for the Control group would be \leq the complication rate for the TAG group. It was estimated that the complication rate for the Control group would be 62.8% with an assumed reduction to 37.5% in the TAG group. The calculations further assumed a 1-sided type I error rate of 0.05 and a power of 86%. Based on these assumptions and criteria, a sample size of 40 evaluable patients in the TAG group and 94 Control subjects was calculated.

A sample size was not calculated for effectiveness.

Study Results

Patients: There were 51 patients (71 \pm 9 years old, 65% male) treated with the modified design of the GORE TAG Thoracic Endoprosthesis. Baseline clinical characteristics were similar between subjects, subjects, and Control subjects except for a higher rate of cancer in TAG subjects (31%) vs. Control subjects (13%).

DTA Aneurysm Assessment: Aorta and aneurysm measurements for subjects and TAG subjects did not differ for aortic diameters immediately proximal to the aneurysm, aortic diameters immediately distal to the aneurysm, aneurysm diameters (61.2 \pm 13.1 mm and 63.8 \pm 15.2 cm, respectively), or aneurysm lengths. A difference was observed in the aorta distal neck length between subjects, and subjects (10.8 cm vs 8.1 cm). Differences for the aorta diameter measures between the subjects and surgical Control subjects were found as they were in the study.

Devices Implanted: A total of 93 endoprostheses were implanted in 51 subjects; most subjects received 1 (33%) or 2 (51%) devices, and no subject received more than 3 devices. Most implanted endoprostheses were 34 mm in diameter (30%), while 28% were 37 mm, 21% were 40 mm, and 22% were 31 mm. The 26 and 28 mm diameter endoprostheses were rarely implanted (2% and 6%, respectively). The distribution of the lengths of the implanted endoprostheses was 15 cm (48%), 10 cm (27%), and 20 cm (24%).

Outcomes:

Safety: The proportion of subjects that experienced ≥ 1 MAE through 30 days post-treatment was significantly less ($p < 0.001$) in 0 subjects (12%) compared to Control subjects (70%). Compared to Control subjects, subjects experienced fewer major bleeding complications (0% vs 53%), pulmonary complications (4% vs 33%), cardiac complications (2% vs 20%), renal complications (0% vs 13%), wound complications (2% vs 12%), and neurologic complications (2% vs 32%). None of the 51 subjects died during the first 30 days (vs. 6% Control subject deaths), and there no aneurysm ruptures.

Minor adverse events. The proportion of subjects who experienced ≥ 1 minor AE through 30 days post-treatment was significantly less in the TAG compared to Control subjects (25% vs. 54%). The TAG subjects experienced fewer minor cardiac complications (2% vs. 16%), and wound complications (0% vs. 11%).

Efficacy: There were no major device-related events (no endoleaks, access failures, occlusion of branch vessel, prosthesis migration, or aneurysm enlargement) through the 30-day follow-up visit in [REDACTED] subjects compared to 6 (4%) subjects in the [REDACTED] cohort. There were 6 (12%) subjects with minor endoleaks in the [REDACTED] subjects, compared to 19 (14%) reported for the [REDACTED] subjects. One subject with a minor proximal endoleak (noted 1-month procedure) and a distal endoleak (noted 92 days-post-procedure) underwent placement of 2 additional Gore TAG Endoprostheses 141 days post-procedure.

Secondary Outcomes: The [REDACTED] subjects experienced a shorter ICU stay ($p < 0.001$) and total hospital stay ($p < 0.001$) than the [REDACTED] Control subjects. In addition, [REDACTED] subjects experienced less procedural blood loss than [REDACTED] subjects.

Wire Fractures: No wire fractures have been observed in the modified devices through 30 days of follow-up.

Protocol Deviations: There were 4 protocol deviations in which the aneurysm was felt to warrant repair but the diameter was less than 2-times the adjacent aorta.

Extended Follow-up: Patient follow-up is ongoing and will continue through 5 years post-treatment.

1.4.2.4 Supplementary Clinical Information

There is an OUS Gore TAG Registry of 114 subjects as of 7/26/04 and a Eurostar Registry (199 patients in progress report of September 2002). There are 3 sponsor-investigator [REDACTED] [REDACTED], high surgical risk patients; and [REDACTED] patients with thoracic aortic catastrophes).

1.5 Review Summary

1.5.1 Non-clinical

The following pre-clinical studies were conducted to compare of the performance of the modified device to the original device design:

Simulated use	testing in straight and angulated aneurysmal models evaluating accessory compatibility, deployment accuracy, device conformability, and resistance to migration
Axial compression	testing characterizing the longitudinal resistance to compression and comparing the results to the original device
Tensile and burst	testing of the graft material to determine adequate tensile and burst strength
In vivo (animal)	testing to evaluate the accessory compatibility, deployment accuracy, device conformability and resistance to migration in a non-aneurysmal ovine thoracic aorta
Dimensional	verification of the delivery catheter, endoprosthesis and the endovascular system to ensure profile, lengths and diameters meet specification
Deployment	testing using a non-flow, tortuous model evaluating accessory compatibility, device conformability and determining "worse-case" deployment forces
Bend radius	testing to characterize the ability of the endoprosthesis to conform to anatomy
Radial expansion	testing to characterize the radial force exerted by the stent during oversizing
Fibril length measurements	ensures the luminal surface microstructure is unchanged
Water entry	Testing to ensure the graft material will not leak

pressure	
Bending fatigue	testing to compare the bending durability of the modified endoprosthesis to the original endoprosthesis
Graft material abrasion	Testing to compare the stronger graft material to the original graft material
Finite element analysis	estimates the expected strains on the wire-frame as a function of oversizing

In all preclinical testing the modified device performed as well or better than the original device, including long-term implant durability testing.

For the PMA application, a complete battery of pre-clinical bench testing results was provided for the modified design of the device. The testing platform was based on the ISO standard for endovascular prostheses. Additional testing beyond that described in the standard was conducted to further evaluate the performance of the device under conditions simulating the clinical environment, such as bending. The testing was comprehensive and the results acceptable. Clarification was requested and received regarding the corrosion properties of the metallic components of the implant. There are no outstanding concerns regarding the bench testing for this device.

The review of the biocompatibility, *in vivo* animal studies, manufacturing and sterilization information (including packaging and shelf-life) have been completed and there are no outstanding issues regarding these parts of the PMA.

The draft Summary of Safety and Effectiveness Data in Appendix I of the panel package includes summaries of the pre-clinical test data provided in the PMA.

Device Integrity

The review of this PMA has included an assessment of device integrity. As with stents used in the vascular system and endovascular grafts used to treat abdominal aortic aneurysms, thoracic endovascular grafts are subject to conditions that may result in a loss of device integrity (e.g., structural failures). Depending on the location and type of the breach in integrity, there may or may not be an immediate or eventual clinical consequence. The original design of the GORE TAG Thoracic Endoprosthesis was associated with a relatively high rate of structural failures. Despite these failures, the clinical results for this design of the device were favorable as compared to the surgical Control group. The parts of the original device that were prone to breaking (i.e., longitudinal spines) were removed in a redesign of the product. Implant durability testing showed that the modified device was superior to the original design. All other parameters measured were comparable or improved for the modified device.

There is a risk of wire fractures in the modified device, though none have been observed in the clinical use of this device. Further, the clinical results for the original design of the device demonstrate that fractures are rarely associated with clinical sequelae. Adequate information has been provided to assess safety and effectiveness with respect to the structural integrity of the device.

1.5.2 Clinical

The sponsor has been asked to address concerns raised regarding the clinical information provided in their PMA, most notably related to the following issues:

- Justification for the proposed intended use and discussion on the strategy for obtaining adequate information to allow for the expansion of the indication to cover additional etiologies (e.g., dissection).
- The rationale for use of 30 day data to justify approval of the Gore TAG and criteria for acceptable 30-day device-related complication rates based on that defined for the pivotal study.
- Clarification on patient allocation and follow-up as well as how missing values (e.g., patient drop-out) were handled in the data analyses.
- The appropriateness of reporting p-values for subgroup analyses in both studies and for the efficacy evaluation for [REDACTED].
- A discussion on the pooling of data across clinical sites.
- Propensity score analysis or similar procedure to evaluate the comparability of treatment groups and a discussion on observed differences in patient groups, such as NYHA classification and proportion of symptomatic aneurysms.
- Submission of electronic data.
- A summary of all clinical data available for the device.
- Clarification on the post-approval evaluation plans and timing of availability of longer-term follow-up for the pivotal and confirmatory patients.
- Submission of a more detailed training plan.

Resolution of these concerns is in progress and an update will be presented at the panel meeting.

1.5.3 Training

The proposed training program is predicated on the training program utilized for the GORE Excluder Bifurcated Endoprosthesis for treatment of AAA and the European release of the TAG device. The program incorporates a tiered approach, based on prior endovascular experience. The most intensive training will be provided to clinicians with experience using AAA endovascular grafts, but not thoracic endovascular grafts. The training program includes a Gore sponsored training course, additional TAG case viewing and Gore supervised training cases.

1.5.3 Post-approval Plan

The sponsor will continue to follow [REDACTED] and [REDACTED] patients out to 5 years in accordance with the original IDE protocols. A study to assess the performance of the device when used to treat other etiologies (e.g., dissections, transections, penetrating aortic ulcers) in addition to aneurysms in patients at high-risk of morbidity and mortality associated with surgical repair is planned to begin in the near future. In total, Gore plans to follow approximately 250 patients post-approval for up to 5 years.

1.6 Summary

All primary safety and effectiveness endpoints were met for the clinical studies reported in the PMA. The rate of neurological complications was considerably less for the TAG patients as compared to the open surgical Control group. No aneurysm ruptures were observed through the 24-month follow-up visit in the Pivotal Study. Aneurysm-related death was only associated with the procedure and not with additional interventions or device failures in both the [REDACTED] and [REDACTED] studies.

The device modifications were made to greatly reduce the risk of fractures in the device. Through a risk analysis, it was determined that these modifications could affect the delivery of the device, but were unlikely to affect the longer-term clinical performance of the device. Given that the majority of clinical events occurred within the first 30 days in the pivotal study, the results of the risk analysis, and the results of pre-clinical testing, a 30-day study was determined to be appropriate to evaluate the modifications. The data from this study confirmed that the clinical performance of the device was not adversely affected by the modifications.

In summary, results of the clinical studies indicate that the GORE TAG Thoracic Endoprosthesis is sufficiently safe and effective compared to open surgical repair in the primary treatment of DTA aneurysms.