I. Overview:

This annual clinical update provides a review of the ongoing experience with the Relay Thoracic Stent-Graft System with Plus Delivery System (P110038), hereafter referred to as RelayPlus, used in the treatment of thoracic aortic aneurysm or penetrating atherosclerotic ulcer covering the time period from September 2, 2022 – September 1, 2023. The original Relay Thoracic Stent-Graft with the Transport delivery system received CE Mark in April 2005 and has been commercially distributed originally in the EU and now exclusively in China. The RelayPlus received CE Mark in 2009 and has subsequently been commercially available globally in the EU, ASPAC including Japan and in Latin America; it has been commercially available in the United States since 2012. In this update, five years of IDE clinical data, 5 years of the Post-Approval Study (PAS) data and over 10 years of worldwide commercial experience is presented. As of this report, the PAS has completed the 5 year follow-up on evaluable subjects.

The Relay Pivotal study involved two delivery system iterations: Transport and Plus. There were no modifications to the Relay Stent-Graft. Ninety-five subjects enrolled in the Pivotal study received the Relay Stent-Graft with Transport delivery system. The Plus delivery system was introduced during the clinical study on September 9, 2009, and the remaining 25 subjects in the Pivotal study, along with all 13 subjects enrolled under Continued Access, were treated with RelayPlus. There were 45 subjects enrolled in the PAS.

The Plus delivery system included the following modifications:
- Hydrophilic coating on the sheath tip
- Higher radiopacity of the sheath tip
- Longer introducer sheath
- Nitinol vs. stainless steel inner catheter to facilitate navigation and alignment

FDA approval of the RelayPlus was granted on September 21, 2012.

PMA Approval Order	https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110038A.pdf
Summary of Safety and Effectiveness (SSED)	https://www.accessdata.fda.gov/cdrh_docs/pdf11/P110038B.pdf
Post Approval Study (PAS) Webpage	https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm?tid=480221
Instructions for Use (IFU)	https://eifu.terumoaortic.com/TAG/US/RPlus?keycode=28-M322150222290U

II. Worldwide Device Distribution:

There have been over 25,000 devices distributed worldwide as part of the IDE, Post-Approval Study and commercially. Approximately 930 RelayPlus have been sold worldwide between September 1, 2022 and September 1, 2023. During this time, a total of 418 devices were shipped within the US, with a total of 92 devices implanted.

III. Clinical Evaluations:

US Pivotal Study:
The Relay Pivotal (Phase II) study was initiated in the US in 2007 and included 120 subjects treated with the Relay Thoracic Stent-Graft (Relay cohort) and 60 surgical control subjects (surgical control

cohort). This study was designed to evaluate the safety and effectiveness of the Relay Thoracic Stent-Graft in subjects with a diagnosed thoracic aortic aneurysm or penetrating atherosclerotic ulcer. The endovascular subjects were followed to 5 years after implantation, with the final subject visit for the Pivotal study occurring in October 2015. Upon enrolling 120 subjects in the Relay cohort, the study was extended under the Continued Access provisions. This study remained open until the Relay device was commercially approved on September 21, 2012. A total of 13 subjects were enrolled in the Continued Access cohort. In the Pivotal cohort, the average length of follow-up for the endovascular subjects was 1257 days (approximately 3.4 years). At the conclusion of the study, 39 subjects of the 53 eligible (74%) completed the final 5-year visit. A 93.2% freedom from aneurysm-related mortality was achieved in the endovascular cohort. There was one conversion to open repair during follow-up. There were no aneurysm ruptures in the treated segment of the aorta. Ten subjects underwent secondary interventions. Complete details are found in the SSED (see link above).

Relay Post Approval Study:

The RelayPlus PAS is a multi-center, prospective study initiated to assess the longer term performance of the RelayPlus Thoracic Stent-Graft, along with an evaluation of device usage and training effectiveness of novice versus experienced implanters. The study involved *de novo* investigational sites that did not participate in the Relay Pivotal study. Selection criteria reflected patient anatomy consistent with the indications for use. The primary endpoint is measured as freedom from ARM at 5 years post-procedure. Aneurysm-related mortality is defined as death from rupture of the descending thoracic aortic aneurysm (DTAA) or penetrating aortic ulcer (PAU), or from any procedure intended to treat the DTAA or PAU. Secondary endpoints for the PAS are the assessment of training effectiveness and the evaluation of major device-related events and major morbidity. A total of 45 patients were enrolled in the study from March 2014 to January 2018. Follow up of these patients is now complete with all evaluable subjects having completed 5 year follow-up. Fifteen (15) subjects have completed the 5 years of follow-up, 12 subjects have expired, 8 were withdrawn by the PI, 6 subjects voluntarily withdrew and 4 are lost to follow-up.

Core-lab reported data from the RelayPlus Post-Approval Study subjects to date:

RelayPlus Post-Approval Study - Core-lab reported data							
	30-days	**1 Year**	**2 Years**	**3 Years**	**4 Years**	**5 Years**	**Total subjects**
Eligible for Follow-up	45	42	36	29	26	19	
Subjects with visit data	42	36	29	25	21	13	
Subjects with CT Scan	42	34	28	23	19	13	
Subjects with X-Ray	41	33	24	19	16	10	
Events							
Aneurysm-related Mortality	4.4% (2/45)	0	0	0	0	0	2
All-cause Mortality	4.4% (2/45)	4.8% (2/42)	5.6% (2/36)	6.9% (2/29)	7.7% (2/26)	10.5% (2/19)	12
Major Adverse Events	6.7% (3/45)	2.3% (1/42)	0	0	0	0	4
Aneurysm Rupture	0	0	0	0	0	0	0
Conversion to Open Surgery	0	0	0	0	0	0	0
All Endoleaks*							
Type Ia	0	0	0	3.4%	0	0	1

RelayPlus Post-Approval Study - Core-lab reported data							
	30-days	**1 Year**	**2 Years**	**3 Years**	**4 Years**	**5 Years**	**Total subjects**
				(1/29)[a]			
Type Ib	0	0	0	3.4% (1/29)[b]	0	0	1
Type II	4.4% (2/45)	2.3% (1/42)	2.8% (1/36)	0	3.8% (1/26)	0	5
Type III	0	0	0	1	3.8% (1/26)[d]	5.3% (1/19)[d]	1
Type IV	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0
Aneurysm Sac Enlargement (> 5 mm)*	0	4.8% (2/42)[c,d]	2.8% (1/36)[d]	6.9% (2/29)[d,e]	7.7% (2/26)[d,e]	5.3% (1/19)[e]	3
Loss of Device Integrity	0	0	0	0	0	0	0
Migration > 10 mm		0	2.8% (1/36)[f]	3.4% (1/29)[a]	0	0	2
Loss of Patency	0	0	0	0	0	0	0
Any Secondary Intervention	0	2.3% (1/42)	0	0	0	0	1

*x is the number of subjects who reported that event, and y is the number of subjects with follow-up/adequate imaging to assess the parameter.

[a] Subject 512-106: Type Ia endoleak detected at 3-year follow-up, with associated caudal migration of the proximal neck and expansion of the proximal aorta. Subject expired 1538 days (~4 years) post implant due to atherosclerotic cardiovascular disease.

[b] Subject 503-101: Type Ib endoleak detected at 3-year follow-up. No migration or aneurysm sac increase.

[c] Subject 502-105: sac increase of 6.3 mm at 1 year, decreased to -5.4 mm from baseline at 2 years, further decreased to -11.8 mm from baseline at 3 years. No migration or endoleak.

[d] Subject 513-103: sac increase of 7.6 mm at 1 year, ongoing at 2, 3 and 4 years. No migration. Type II endoleak detected at 4 years which was reclassified by the Core Lab as a Type III endoleak when seen at the 5-year follow-up. No secondary intervention performed to date

[e] Subject 512-101: sac increase of 6.1 mm at 3 years, persisted at 4 and 5 years, possibly due to secondary aneurysm present below treated area. No migration or endoleak.

[f] Subject 502-104: experienced cranial migration of the distal neck at 2 years, likely attributed to lengthening of the aorta. Subject expired 1889 days (~5 years) post implant due to intracerebral hemorrhage.

Two subjects completed the four-year time point and 1 subject completed the 5-year time point during this reporting period. No Core-lab identified events were reported and no secondary interventions were collected.

Commercial access to RelayPlus is granted if the physician possesses the required experience needed to perform an endovascular procedure and has completed the required in-service device training for new users. Delivery and deployment rates for experienced versus novice implanters have been evaluated and while the number of subjects treated by experienced implanters remains small, there appears to be no notable differences in outcomes compared to those of novice implanters.

Procedural parameters were also compared, and experienced implanters had slightly longer procedural and fluoroscopy time, with slightly less blood loss and contrast used. Procedural related MAEs were slightly higher in the experienced group, however, the experienced centers consistently perform implants on challenging anatomy, which present a higher risk for MAEs. Overall, the review does not support any clinically meaningful differences between subjects treated by experienced vs novice users in terms of patient demographics or outcomes providing evidence of training effectiveness.

IV. Worldwide Recalls, Safety Communications and Field Safety Notices:

There have been no US recalls, safety communications and/or Field Safety Notices issued for RelayPlus during this reporting period.

In 2014, there was a Field Safety Notice outside the US as a result a small number of cases where the inner sheath of the delivery system had not fully exited from the outer sheath as expected. A Field Safety Notice was issued recommending additional verification steps to avoid potential advancement or deployment difficulties. The Instructions for Use (IFU) were subsequently updated to include the recommendations.

In February 2021, a Field Safety Notice outside the US was issued to address discrepancies in the RelayPlus OUS IFU distal landing zones and select device characteristics. The risk assessment determined there was no associated patient risk, however distributors were notified for awareness pending implementation of a corrected Instructions for Use.

V. Worldwide Commercial Experience:

RelayPlus is distributed globally and receives feedback/learnings from this worldwide commercial use. The following table summarizes the associated complaints for this Annual Report timeframe.

RelayPlus Complaints: September 1, 2022 – September 1, 2023		
Failure Mode Description (internal code)	**# of complaints / failure mode**	**MDR Filed**
Clinical Observations		
Type I Endoleak (056, 099)	4	Yes
Type III Endoleak (056, 101), inaccurate deployment of the stent-graft / stent-graft misplacement (037)	1	Yes
Dissection found post-procedure (058), infection detected post-procedure (073)	1	Yes
Delivery / Deployment Observations		
Device preparation difficulty (032)	1	No
Unable to advance device over the guidewire (094)	1	No

Based on the review of complaints, the reported Clinical Observations remain stable from the previous Annual Report and do not demonstrate an observable trend. Reported endoleaks increased by 1 and the occurrence levels remain within the values estimated and assessed within the Risk Management System. Endoleaks are among the expected adverse events associated with TEVAR. There were no reports of death resulting from the adverse events, perforations or rupture during this reporting period and only one reported dissection.

The Delivery/Deployment-related complaints remain similar to the previous Annual Report with no observable trends. Field performance remains within the expected occurrence levels.

Bolton Medical will continue its diligence in monitoring and investigating product complaints and take necessary actions, as needed, and concludes that the benefits of using the RelayPlus Thoracic Stent-Graft system continue to outweigh the associated risks.

VI. Explant Analysis:

Through the course of the investigational phase and following commercialization, eight explants have been analyzed. None have shown any obvious damage associated with the device. Bolton Medical recommends routine imaging follow-up to ensure subjects are evaluated for conditions that may necessitate intervention. An additional three stent-grafts were partially/fully explanted, however, were not returned to Bolton Medical for inspection. There were no explants reported during this reporting period.

VII. Literature Review:

There have been 3 publications with information on the Relay/RelayPlus device since the last update. Some are not focused on outcomes with Relay but report overall outcomes of at least some procedures performed with Relay. These articles were considered of purely scientific interest and are not being used to make changes to practices or procedures. The RelayPlus device is indicated for the endovascular repair of fusiform aneurysms and saccular aneurysms/penetrating atherosclerotic ulcers in the descending thoracic aorta. Some of the uses described in the publications are outside the approved indications.

Article Citation	Description and Impact
Gennai, Stefano, Nicola Leone, Luigi A. M. Bartolotti, Francesco Andreoli, Ginevra Pizzarelli, and Roberto Silingardi. "Learning Curve and Long-Term Outcomes of Thoracic Endovascular Repair With the Relay Stent-Graft." Journal of Endovascular Therapy, November 16, 2022, 15266028221136450. https://doi.org/10.1177/15266028221136450 .	RelayPlus was used in 94.1% of cases (n=207) versus 5.9% for RelayPro. 10 procedures with the Relay stent-graft were required for the slope to remain steadily below the 23.1% learning composite outcome threshold. Implanting physicians involved in the study had already performed tens of TEVARs and hundreds of endovascular repairs before employing the Relay platform. This could have influenced such a short learning curve. The primary outcome was the learning curve analysis using the cumulative sum chart method. The secondary outcomes, presented as early (Q1–Q2) versus latest (Q3–Q4) quartiles of experience, were 30-day major adverse events (MAEs); procedural details (additional maneuvers, operative and fluoroscopy time, and contrast volume); 30-day clinical success; endoleak; aorta-related reintervention; and overall and aorta-related survival. Thirty-day MAEs were registered in case of complications such as cardiologic (myocardial infarction or new-onset arrythmia), neurologic (stroke and paraplegia), embolic (pulmonary, limb, or bowel), hemorrhage, respiratory failure, renal function worsening (serum creatinine increase >2 mg/dL), and aortic dissection. The Relay stent-graft presented satisfactory long-term results along with a short learning curve.
Sato, Tomohiro, Hiroshi Banno, Shuta Ikeda, Yohei Kawai, Takuya Tsuruoka, Masayuki Sugimoto, Kiyoaki Niimi, Akio Kodama, and Kimihiro Komori. "Severe Tortuosity of the Distal Descending Thoracic Aorta Affects the Accuracy of Distal Deployment During a Thoracic Endovascular Aortic Repair." Journal of Endovascular Therapy, December 2, 2022,	Three (n=3) RelayPlus devices were used in this retrospective review. Study concluded that severe tortuosity in the distal descending thoracic aorta is associated with a malpositioned and tilted distal end of the stent-graft. TEVAR for paradiaphragmatic thoracic aortic aneurysms requires accurate distal landing. The analysis revealed that the greater curve to the straight-line ratio (G/S ratio) was associated to affects the malposition of the stent graft, defined as being deployed more than 10 mm away from the target vessel. Further, a comparative analysis based on the G/S

Article Citation	Description and Impact
15266028221141024. https://doi.org/10.1177/15266028221141023	ratio demonstrated that severe aortic tortuosity was associated with a more distal and tilted deployment of the stent graft.
Gennai, Stefano, Francesco Andreoli, Nicola Leone, Luigi Alberto Maria Bartolotti, Tea Covic, and Roberto Silingardi. "BAlloon Inducted Re-Lamination and False LUmen Thrombosis (BAILOUT) in Chronic Type B Aortic Dissection: Technique and Long-Term Results." Annals of Vascular Surgery, January 13, 2023. https://doi.org/10.1016/j.avsg.2022.12.091	Aim of this study was to evaluate the safety, feasibility, and effectiveness of the BAlloon Inducted reLamination and false lUmen Thrombosis (BAILOUT) as a simple technique to address the retrograde false lumen (FL) perfusion and subsequent aneurysmatic degeneration of the thoracic aorta due to a stent-graft crimped in a small true lumen in chronic Type B dissections. An observational, retrospective, single-center study analyzing a nonconsecutive cohort of 8 patients affected by chronic type B aortic dissections already treated with thoracic endovascular repair (n=6 Relay Plus; n=2 Zenith Cook) and with an FL lumen backflow corrected with BAILOUT between 2006 and 2020. After a standard distal extension of the previously implanted graft, the distal end of the graft area was ballooned to completely rupture the dissection lamella to relaminate the aorta hindering the FL backflow. The technical and clinical success achieved was 100% with the complete interruption of FL backflow stating the safety and feasibility of the BAILOUT technique. No early procedure reinterventions were recorded and during a median follow-up of 62.5 months [interquartile range 43.2e94.1], only 1 death unrelated to the procedure was recorded. Freedom from aortic-related adverse events at 1 month, 3 months, 1 year, 5, and 7 years was 87.5%, 62.5%, 62.5%, 62.5%, and 62.5%, respectively. During the follow-up, no one increment of the diameter of the thoracic aorta was documented and all the patients at 3 years of computed tomography angiography showed a complete FL thrombosis. The BAILOUT technique demonstrates to be safe and feasible in this small cohort of patients as a simple and quick way to overcome the issue of false lumen backflow in chronic type B dissection. Small cohort and retrospective designs were limitations of the study.

VIII. Conclusion:

Based on available clinical study data and world-wide clinical experience to date, endovascular therapy with the RelayPlus Thoracic Stent-Graft System continues to be a viable treatment option for fusiform aneurysms and saccular aneurysms/penetrating atherosclerotic ulcers in the descending thoracic aorta.

Adverse Event Reporting:

As indicated in the Instructions for Use, adverse events or complaints should be reported by contacting 1-855-726-5866 (1-855-7BOLTON). Accurate and timely reporting of adverse events by the physician users to the device manufacturer and FDA (MedWatch Form 3500) is critical for monitoring device performance and detection of potential device-related safety issues.

Patient Follow- Up and Selection:

Regular follow-up of all patients treated with the RelayPlus Thoracic Stent-Graft System is required. Physicians should tailor patient follow-up to the needs and circumstances of each individual patient following endovascular graft placement. Patients should be regularly monitored for endoleaks, lesion growth, or changes in the structure or position of the endovascular graft. At a minimum, annual imaging is recommended.