3 Summary

Title

LifeStent™ post-market clinical follow-up (PMCF) study: a retrospective 5-year assessment

Introduction

The device evaluated in this investigation is composed of a group of 3 devices referred to as the "LifeStent Family". The LifeStent Family includes the LifeStent™/LifeStent™ XL Vascular Stent, the LifeStent™ Solo Vascular Stent, and the LifeStent™ 5F Vascular Stent System. These devices are all commercially available Conformité Européenne (CE)-marked devices. Devices of the LifeStent Family are indicated to be used for the treatment of atherosclerotic lesions in the superficial femoral artery (SFA) and popliteal artery in adult patients with de-novo or restenotic lesions in these vessels.

This PMCF retrospective investigation was being conducted to collect long-term data (up to 5 years of follow-up) on the safety and effectiveness of the LifeStent Family of devices when used within their indications for use to treat atherosclerotic lesions in the SFA and popliteal artery.

The data complement previously generated clinical data on the devices and will support the ongoing evaluation of their safety and effectiveness.

Clinical Investigation Start and End

Investigation initiation: 22-May-2024 (first subject enrolled)
Investigation completion: 17-Jan-2025 (data entry completed for last subject)

Investigated Period

First subject's baseline entry: 05-Aug-2013
Last subject's date of study completion: 13-Dec-2024

Objectives and Endpoints

Objectives	Endpoints
Primary	***Primary safety***
• Assess the long-term clinical safety and effectiveness attributes of the LifeStent Family of devices when used for the treatment of atherosclerotic lesions in the SFA and popliteal artery	• Freedom from implant-related complications through 36 months post-index procedure. ***Primary effectiveness*** • Freedom from target lesion revascularization (TLR) through 36 months post-index procedure.
Secondary safety	***Secondary safety***
• Assessing the long-term safety profile of the device.	• Freedom from major adverse events (MAEs) through 12-, 24-, 36-, 48-, and 60-months • Freedom from implant-related complications through 12-, 24-, 48-, and 60-months post-index procedure.
Secondary effectiveness Assessing the effectiveness of the study device with respect to its reintervention profile long-term.	***Secondary effectiveness*** • Freedom from TLR through 12-, 24-, 48-, and 60-months post-index procedure. • Freedom from target vessel revascularization (TVR) through 12-, 24-, 36-, 48-, and 60-months post-index procedure.
Exploratory	***Exploratory effectiveness***
• Assess the long-term impacts on a patient's symptoms after treatment with the study device through 60 months.	• Sustained clinical success through 12-, 24-, 36-, 48-, and 60-months post-index procedure.

Subjects

Number of subjects (total and for each treatment) planned and analyzed:

- Planned: 112 subjects who were treated with a device of the LifeStent Family no later than January 2019
- Analyzed sets: 116 subjects entered the investigation and 112 eligible subjects were enrolled.[1] For subjects who objected to participation, no data (except subject identification numbers) were entered in the electronic case report form (eCRF).

Methods

Overall Design

This investigation was a retrospective PMCF data collection evaluating 5 years of post-implantation real-world data collected during the routine clinical care of subjects who were

[1] Four subjects were entered in the eCRF, but 2 subjects objected to participation and 2 subjects were considered screening failures and not included in the Enrolled Population.

treated with devices of the LifeStent Family for atherosclerotic lesions in the SFA and popliteal artery.

Long-term safety and effectiveness clinical outcomes were assessed as part of this investigation including freedom from: TLRs, implant-related complications, MAEs, and TVRs. No control was used in this PMCF investigation, as it aimed to provide insight into the long-term safety and effectiveness of the devices and to complement the existing data.

Diagnosis and Criteria for Inclusion

1. The adult subject (≥18 years old) provided written informed consent (or where allowable the non-opposition process was followed on subjects that were not deceased)

   Note: Subjects may be enrolled without signing a consent form only if the responsible ethics committee has waived the requirement and written documentation about this decision has been provided to the Investigator and the Sponsor, or where allowable according to the local regulations

2. The subject had evidence of a hemodynamically relevant stenosis or restenosis ≥50% (as determined by the Investigator's visual estimate) or occlusion in the SFA or popliteal artery and the vessel diameter was appropriate for treatment with one of the available investigational device implant sizes

3. The subject's lesion(s) was (were) treated with one or more of the LifeStent Family of devices no later than January 2019

4. The subject had ≥5 years of relevant follow-up information available for the initially treated target lesion(s). At minimum the following key clinical data had to be available through 36 months:

   a) Information on investigational device implant-related complications as defined for the primary safety endpoint

   b) Information on MAEs

   c) Information on reinterventions/revascularizations of the target lesion and/or target vessel

   d) Clinical presentation status (Rutherford classification, Fontaine classification and/or assessment of clinical symptoms related to peripheral artery disease [PAD])

Investigational Devices

The "LifeStent Family" is composed of the following 3 devices:

- LifeStent™/LifeStent™ XL Vascular Stent (Unique Device Identifier [UDI]: 038290WMKVGHRGMJ)
- LifeStent™ Solo Vascular Stent (UDI: 0801741YVYSRJEXMR)
- LifeStent™ 5F Vascular Stent System (UDI: 0801741VPMYNMUMED)

Each device contains laser-cut self-expanding nitinol tubing with identical material composition and laser-cut pattern of the stent. The devices differ in the radiopaque markers on their ends, in the range of stent lengths and diameters available, and in the system designs and mode of deployment of the delivery systems. Based on the similarity of the devices, the resultant clinical data from prior studies, and given that the delivery systems were all validated, the differences were concluded not to be clinically relevant to the long-term outcomes of the LifeStent Family of devices.

Reference Product

Due to the single-arm design, and the aim to collect data on long-term safety and effectiveness of the investigational devices, no reference device was included.

Statistical Methods

No hypothesis testing was conducted for this investigation. The primary effectiveness and safety endpoints (freedom from TLR and freedom from implant-related complications) and several secondary endpoints (including freedom from: MAEs, TLR, and TVR) were time-to-event variables. The Kaplan-Meier method was applied to these variables to estimate the risk rate or survival rate at the defined timepoints of interest. In addition, descriptive statistics were applied to summarize endpoints.

Summary statistics for categorical variables included frequency counts and proportions. For continuous variables mean, median, standard deviation, minimum and maximum were calculated. Additionally, 95% confidence intervals were provided for proportions for categorical variables and for means of continuous variables.

Results

Results – Subjects

Subject Disposition

Data of 116 subjects were entered in the database, of which 112 subjects (96.6%) were eligible and analyzed as part of the Enrolled Population, 78 subjects at Site 1 (France) and 34 subjects at Site 2 (Germany).

All 112 eligible subjects (100%) in the Enrolled Population had data records at Baseline and the index procedure, while data for the 12-, 36-, and 60-month visits were available for 105 (94%), 104 (93%), and 111 subjects (99%), respectively. At the 24- and 48-months visits, slightly fewer subjects had data entries (86% and 78%, respectively). For all post-index procedure visits, a window of ±6 months was applied.

Regarding individual subject data, irrespective of the 12-month window applied for the corresponding timepoints, all 112 subjects (100%) had data available for at least 36 months post-index procedure,[2] and 69 subjects (62%) had data available for at least 60 months post-index procedure.

[2] I.e. for subjects with missing 36-month data, data beyond 36 months were available.

Demographics and Baseline Characteristics

The Enrolled Population included more men than women (76% vs 24%). Subjects had a median age of 66 years at the index procedure, ranging from 47 to 95 years. The median body mass index was 26 kg/m² (ranging from 14.5 to 41.4 kg/m²). Of the subjects with the corresponding data available, 67% (37 of 55 subjects) had severe claudication (Rutherford Classification 3) and 44% (34 of 78 subjects) had claudication at a distance <200 meters (Fontaine Classification Stage IIB). The median ankle-brachial index (ABI) at the target limb of 72 subjects with available data was 0.7 (ranging from 0 to 2.8) [3]. For 4 subjects toe-brachial index data were available, which ranged from 0.1 to 0.4.

Index Procedure

The target lesion was located in the SFA in 81% of subjects and in the popliteal artery in 19%, with most subjects (94%) having a new lesion and few subjects a reoccurring lesion (6%). In 75% of subjects the lesion type was stenosis: alone (59%), combined with thrombosis (13%), or with occlusion (4%). The median total target lesion length was 100 mm (ranging from 20 mm to 400 mm) with a median stenosis of 100% (ranging from 50% to 100%) before the index procedure, and a reference vessel diameter of 6 mm (ranging from 5 mm to 8 mm).

The clinical indicators for the intervention (alone or in combination) included PAD symptoms, increase in Rutherford or Fontaine Classification, and change in ABI >0.1. Worsening in PAD symptoms was the predominant indicator (in 84% of subjects).

In all 112 eligible subjects, at least 1 and up to 5 devices were successfully deployed during the index procedure. In total, subjects received 183 stents of the models LifeStent/LifeStent XL Vascular Stent or LifeStent Solo Vascular Stent either alone or in combination. One subject had a LifeStent/LifeStent XL implanted in combination with another stent that was not an investigational device, but its use was permitted according to the LifeStent Family instructions for use. The median stent diameter was 6 mm, ranging from 5 mm to 8 mm, with a median stent length of 80 mm, ranging from 20 mm to 200 mm.

Results - Effectiveness

The analysis of the **primary endpoint**, freedom from TLR through 36 months post-index procedure, showed a Kaplan-Meier rate for freedom from TLR of 72.3%, indicating that 81 subjects had no TLR record from the index procedure through 36 months post-index procedure, with no censored subjects.

Of the 31 subjects (28%) with TLRs, most subjects had 1 TLR (23 subjects), with few subjects (1 to 5 subjects) having up to 6 TLRs within 36 months post-index procedure.

The Kaplan-Meier rate for freedom from TLR at 36 months at Site 1 was 78% at Site 1 and of 59% at Site 2.

[3] A systolic ABI of zero was possible and may have been caused by ischemia of the leg and/or by other anatomical factors.

The Cox regression analysis for poolability of the sites indicates a statistically significant site effect (hazard ratio = 2.2, p = 0.0170).

Subgroup analyses on the primary endpoint showed a difference in Kaplan-Meier rates for freedom from TLR of more than 10% in subjects with target lesions lengths of ≤10 cm vs >10 cm (81% vs 61%), in subjects with severe calcification vs no, mild, or moderate calcification (83% vs 67%), and in male vs female subjects (78% vs 56%).

Analysis of the **secondary endpoints** freedom from TLR through 12-, 24-, 48-, and 60-months and freedom from TVR through 12-, 24-, 36-, 48-, and 60-months post-index procedure showed that the Kaplan-Meier rate for freedom from TLR steadily decreased over time from 87% at 12 months to 67% at 60 months post-index procedure. At 60 months, 45 subjects still showed freedom from TLR, while for 37 subjects one to several TLR(s) was (were) performed, and 30 subjects were censored. The main indicator for the interventions was worsening in PAD symptoms.

Similarly like for TLRs, the Kaplan-Meier rate for freedom from TVR steadily decreased over time from 83% at 12 months to 60% at 60 months post-index procedure. At 60 months, 39 subjects still showed freedom from TVR, while for 45 subjects a target vessel re-intervention occurred previously, and 28 subjects were censored. Like for TLRs, the main indicator for performing TVRs was worsening in PAD symptoms.

The **exploratory endpoint** was sustained clinical success through 12-, 24-, 36-, 48-, and 60-months post-index procedure. Sustained clinical success was defined as sustained cumulative improvement from the baseline clinical presentation (i.e. before the index procedure) as evaluated by the Investigator through the use of Rutherford Classification, Fontaine Classification, and/or the assessment of clinical symptoms related to PAD. The percentage of subjects showing sustained clinical success was 86% at 12 months post-index procedure, and decreased over time to 43% at 60 months post-index procedure.

Results - Safety

The **primary safety** analysis at 36 months post-index procedure showed a Kaplan-Meier rate for freedom from implant-related complications of 96.4%, indicating that 108 subjects had no implant-related complication record (stent infection, stent migration, stent kinking/collapse or clinically relevant stent fracture) from the index procure through 36 months post-index procedure. In 4 subjects (3.6%), clinically relevant stent fractures were reported. All these events were also reported as device deficiencies.

The Cox regression analysis for poolability of the sites indicated no statistically significant site effect.

Subgroup analyses on the primary safety endpoint showed a difference between groups of less than 10% in all subgroups.

Secondary endpoint analyses included freedom from MAEs through 12-, 24-, 36-, 48-, and 60-months post-index procedure and from implant-related complications through 12-, 24-, 48-, and 60-months post-index procedure.

The Kaplan-Meier rate for freedom from MAE steadily decreased over time from 87% at 12 months to 73% at 60 months post-index procedure. At 60 months, 49 subjects still showed freedom from MAEs, while 30 subjects experienced an MAE previously. Most of the reported MAEs (by at least 5 subjects) were vascular stent thrombosis, vascular stent occlusion, cerebrovascular accident, and myocardial infarction.

The Kaplan-Meier rate for freedom from implant-related complications slightly decreased over time from 98% at 12 months to 96% at 48 months and 60 months post-index procedure. At 60 months, 66 subjects still showed freedom from implant-related complications, while for 5 subjects an implant-related complication occurred previously.

In all 5 subjects (4.5%) who had an implant-related complication within 60 months post-index procedure, stent fractures (preferred term: device breakage) were reported that were also recorded as device deficiencies.

Overview of Adverse Events (Enrolled Population, N = 112)

	Enrolled Population (N = 112)	
	n_{AE}	**N (%)**
Any AE	200	74 (66.1)
Any SAE	173	64 (57.1)
Any ADE	35	25 (22.3)
Any SADE	25	18 (16.1)
Any AE related to the procedure	12	10 (8.9)
Any SAE related to the procedure	9	7 (6.3)

ADE = adverse device effect, AE = adverse event, SADE = serious adverse device effect, SAE = serious adverse event, N = number of subjects, n_{AE} = number of adverse events.

In total, 200 adverse events (AEs) were reported in 74 (66%) subjects, with 35 of these AEs in 25 subjects (22%) deemed at least possibly related to the device by the Investigator and categorized as adverse device effect (ADEs). Among 200 AEs observed, 173 events (87%) reported in 64 subjects (57%) were serious adverse event (SAEs), with 25 of these SAEs in 18 subjects (16%) deemed at least possibly related to the device by the Investigator and categorized as serious ADEs (SADEs). SADEs included vascular stent stenosis and vascular stent thrombosis (9 events each), vascular stent occlusion (4 events), and impaired healing, peripheral artery thrombosis and peripheral embolism (1 event each).

Of the total 200 AEs, 12 AEs reported in 10 subjects (9%) were related to the procedure, and 9 of these events reported in 7 subjects (6%) were SAEs. Procedure-related SAEs included peripheral artery thrombosis (3 events), vascular stent thrombosis (2 events), and impaired healing, vascular stent stenosis, vascular access site pseudoaneurysm and vascular pseudoaneurysm (1 event each).

6 events of stent fracture (preferred term: device breakage) occurred in 5 subjects (5%) and were categorized as device deficiency (DD). In 4 of the 5 subjects, the DD occurred within 36 months post-index procedure and affected the primary endpoints. All DDs were associated with AEs that were resolved after reinterventions at the target lesions.

This retrospective investigation excluded subjects who were deceased at the time of enrollment, thus, no data on deaths were collected.

Conclusions

- No major protocol deviations having an impact on the analysis sets or on (primary) effectiveness results were reported.
- The devices of the LifeStent Family showed long-term effectiveness and safety through 60 months post-index procedure consistent with pre-defined acceptance criteria based on the literature and as outlined in the Clinical Evaluation Reports.
- The primary efficacy endpoint, freedom from TLR through 36 months post-index procedure, showed a Kaplan-Meier rate of 72.3%
- Subgroup analyses showed a trend for better performance (>10% difference) in subjects with target lesions of ≤10 cm vs >10 cm, in subjects with severe calcification vs no, mild, or moderate calcification, and in men vs women.
- Kaplan-Meier rates of freedom from TLR and TVR through 60 months post-index procedure were 67% and 60%, respectively.
- 86% of subjects showed sustained clinical success at 12 months, and 43% at 60 months.
- The primary safety endpoint, freedom from implant-related complications through 36 months post-index procedure, showed a Kaplan-Meier rate of 96.4%.
- The Kaplan-Meier rate for freedom from MAEs was 73% at 60 months post-index procedure and for freedom from implant-related complications 96% from 48 months post-index procedure onwards.
- In total, 200 AEs were reported in 74 (66%) subjects, of which 35 AEs in 25 subjects (22%) were ADEs.
- 25 SAEs in 18 subjects (16%) were SADEs, including vascular stent stenosis and vascular stent thrombosis (9 events each), vascular stent occlusion (4 events), and impaired healing, peripheral artery thrombosis and peripheral embolism (1 event each).
- 6 device deficiencies occurred in 5 subjects (5%), all of which were stent fractures associated with AEs prompting target lesion revascularization.