A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial

*William A Gray, Koen Keirse, Yoshimitsu Soga, Andrew Benko, Anvar Babaev, Yoshiaki Yokoi, Henrik Schroeder, Jeffery T Prem, Andrew Holden, Jeffrey Popma, Michael R Jaff, Juan Diaz-Cartelle, Stefan Müller-Hülsbeck, on behalf of the IMPERIAL investigators**

Summary

Background The clinical effect of a drug-eluting stent in the femoropopliteal segment has not been investigated in a randomised trial with a contemporary comparator. The IMPERIAL study sought to compare the safety and efficacy of the polymer-coated, paclitaxel-eluting Eluvia stent with the polymer-free, paclitaxel-coated Zilver PTX stent for treatment of femoropopliteal artery segment lesions.

Methods In this randomised, single-blind, non-inferiority study, patients with symptomatic lower-limb ischaemia manifesting as claudication (Rutherford category 2, 3, or 4) with atherosclerotic lesions in the native superficial femoral artery or proximal popliteal artery were enrolled at 65 centres in Austria, Belgium, Canada, Germany, Japan, New Zealand, and the USA. Patients were randomly assigned (2:1) with a site-specific, web-based randomisation schedule to receive treatment with Eluvia or Zilver PTX. All patients, site personnel, and investigators were masked to treatment assignment until all patients had completed 12 months of follow-up. The primary efficacy endpoint was primary patency (defined as a peak systolic velocity ratio ≤2·4, without clinically driven target lesion revascularisation or bypass of the target lesion) and the primary safety endpoint was major adverse events (ie, all causes of death through 1 month, major amputation of target limb through 12 months, and target lesion revascularisation through 12 months). We set a non-inferiority margin of –10% at 12 months. Primary non-inferiority analyses were done when the minimum sample size required for adequate statistical power had completed 12 months of follow-up. The primary safety non-inferiority analysis included all patients who had completed 12 months of follow-up or had a major adverse event through 12 months. This trial is registered with ClinicalTrials.gov, number NCT02574481.

Findings Between Dec 2, 2015, and Feb 15, 2017, 465 patients were randomly assigned to Eluvia (n=309) or to Zilver PTX (n=156). Non-inferiority was shown for both efficacy and safety endpoints at 12 months: primary patency was 86·8% (231/266) in the Eluvia group and 81·5% (106/130) in the Zilver PTX group (difference 5·3% [one-sided lower bound of 95% CI –0·66]; p<0·0001). 259 (94·9%) of 273 patients in the Eluvia group and 121 (91·0%) of 133 patients in the Zilver PTX group had not had a major adverse event at 12 months (difference 3·9% [one-sided lower bound of 95% CI –0·46]; p<0·0001). No deaths were reported in either group. One patient in the Eluvia group had a major amputation and 13 patients in each group required target lesion revascularisation.

Interpretation The Eluvia stent was non-inferior to the Zilver PTX stent in terms of primary patency and major adverse events at 12 months after treatment of patients for femoropopliteal peripheral artery disease.

Funding Boston Scientific.

Published **Online** September 22, 2018 http://dx.doi.org/10.1016/S0140-6736(18)32262-1

See **Online/Comment** http://dx.doi.org/10.1016/S0140-6736(18)32339-0

*Investigators listed in appendix

Lankenau Heart Institute, Wynnewood, PA, USA (W A Gray MD); **Regional Hospital Heilig Hart Tienen, Tienen, Belgium** (K Keirse MD); **Kokura Memorial Hospital, Kitakyushu, Japan** (Y Soga MD); **Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada** (A Benko MD); **New York University Medical Center, New York, NY, USA** (A Babaev MD); **Kishiwada Tokushukai Hospital, Osaka, Japan** (Y Yokoi MD); **Center for Diagnostic Radiology and Minimally Invasive Therapy, The Jewish Hospital Berlin, Berlin, Germany** (H Schroeder MD); **Aultman Hospital, North Canton, OH, USA** (J T Prem MD); **Auckland City Hospital, Auckland, New Zealand** (A Holden MD); **Beth Israel Deaconess Medical Center, Boston, MA, USA** (J Popma MD); **VasCore, Massachusetts General Hospital, Boston, MA, USA** (M R Jaff DO); **Harvard Medical School, Boston, MA, USA** (M R Jaff); **Boston Scientific, Marlborough, MA, USA** (J Diaz-Cartelle MD); **and Diaconess Hospital Flensburg, Flensburg, Germany** (S Müller-Hülsbeck MD)

Correspondence to: Dr William A Gray, Lankenau Heart Institute, Wynnewood, PA 19096, USA **grayw@mlhs.org**

See **Online** for appendix

Introduction

Lifestyle-limiting claudication is a common manifestation of lower-extremity atherosclerotic peripheral artery disease and is increasing in prevalence because of the ageing population and rise in number of patients with diabetes.[1] Although pharmacotherapy (eg, cilostazol) and supervised exercise therapy might be effective in improving pain-free walking distance, a randomised study[2] has shown that intervention with stent implantation improves patient quality of life, including improvements in pain and symptoms, reduced physical limitations, and increased walking distance, compared with optimal medical care or supervised exercise.

Given that the risks related to percutaneous intervention for claudication are generally low, it is preferentially offered as an initial therapy for claudication and critical limb ischaemia, which has resulted in reduced lengths of hospital stay, fewer amputations, and decreased procedural morbidity and mortality compared with surgical intervention.[3] Although a wide variety of devices are available to revascularise the lower-extremity arterial system, the durability of these endovascular

Research in context

Evidence before this study

We searched PubMed using the search terms "drug-eluting stent", "femoral artery", and "peripheral arterial disease" for papers published up to June 25, 2018, without language restrictions. We identified five systematic reviews and clinical study reports from 18 unique studies of drug-eluting stents for treatment of de-novo or restenotic (non-stent) lesions of the superficial femoral artery or proximal popliteal artery, including one large randomised controlled trial comparing paclitaxel-coated stent use with percutaneous transluminal angioplasty. Study designs for two additional randomised studies of drug-eluting stents were also found during our search. In the global Zilver PTX Randomized Trial, patients who had primary treatment with a Zilver PTX stent had a higher 12-month primary patency rate than did those who received percutaneous transluminal angioplasty (83·1% *vs* 32·8%; p<0·001). No randomised study comparing two drug-eluting stents in this arterial segment was identified.

Added value of this study

To our knowledge, IMPERIAL is the first randomised controlled trial to compare two drug-eluting stents for treatment of femoropopliteal arterial segment lesions. We found that the paclitaxel-eluting, polymer-coated Eluvia stent was non-inferior to the paclitaxel-coated, polymer-free Zilver PTX stent in maintaining primary patency at 12 months after implantation, and had a similar safety profile. This randomised trial with a clinically relevant comparator contributes level 1 evidence to support the use of drug-eluting stents to treat lower-extremity peripheral artery disease.

Implications of all the available evidence

The findings support the effectiveness of the longer paclitaxel elution profile of the Eluvia stent in preventing restenosis while maintaining similar safety to a contemporary comparator.

interventions can be low, especially in patients with long, complex lesions.

Accordingly, antiproliferative therapies based on paclitaxel have been developed to extend the durability of these procedures and reduce the number of re-interventions required for restenosis. Drug-coated balloons deliver paclitaxel in a single burst at the time of intervention, and the drug remains in the tissue long enough to affect patency.[4–7] Although effective, balloon-based drug delivery does not have the capacity to scaffold the vessel, which is a common requirement in patients with long lesions or who have calcified femoropopliteal disease.[8] To address this issue, a previous study[9] compared a polymer-free, paclitaxel-coated, self-expanding, slotted-tube, nitinol stent (Zilver PTX; Cook Corporation, Bloomington, IN, USA) with both standard percutaneous transluminal angioplasty and bare-metal stents and showed significant reductions in the need for target lesion revascularisation and significant improvements in long-term patency.

The IMPERIAL randomised study sought to compare the safety and efficacy of the novel paclitaxel-eluting, durable-polymer-coated Eluvia stent (Boston Scientific, Marlborough, MA, USA) with the established Zilver PTX stent. Eluvia delivers paclitaxel over a longer duration than Zilver PTX, which is important considering that the observed peak of restenosis in the femoropopliteal arteries is 10–12 months.[10] Eluvia has already shown efficacy in the MAJESTIC first-in-human study,[11] which found 96·4% primary patency at 1 year.

Methods

Study design and participants

IMPERIAL is a global, prospective, randomised, controlled, single-blind, non-inferiority study in patients enrolled at 65 community hospitals, academic hospitals, university hospitals, and referral centres in Austria, Belgium, Canada, Germany, Japan, New Zealand, and the USA (appendix). Two concurrent single-group (Eluvia only) substudies were done: a non-blinded, non-randomised pharmacokinetic substudy and a non-blinded, non-randomised study of patients with long lesions (>140 mm). Results of the randomised controlled trial and the pharmacokinetic substudy are reported here.

Eligible patients were aged 18 years or older and had symptomatic lower-limb ischaemia, defined as Rutherford category 2, 3, or 4,[12] and stenotic, restenotic (treated with a drug-coated balloon >12 months before the study or standard percutaneous transluminal angioplasty only), or occlusive lesions in the native superficial femoral artery or proximal popliteal artery, with at least one infrapopliteal vessel patent to the ankle or foot. Patients had to have stenosis of 70% or more (on visual angiographic assessment), vessel diameter between 4 mm and 6 mm, and total lesion length between 30 mm and 140 mm. Full inclusion and exclusion criteria are provided in the appendix. Eligibility criteria were identical for the randomised trial and the pharmacokinetic substudy. Patients provided written informed consent to participate in the study.

The trial was done in a coordinated manner, with regulatory agencies from the various countries involved to achieve device approval assuming the prespecified endpoints were satisfied. Ethical approval of the study protocol was obtained from the institutional review board, independent ethics committee, or research ethics board at each study site.

Randomisation and masking

Patients were randomly assigned (2:1) to implantation of either a paclitaxel-eluting polymer stent (Eluvia) or a

paclitaxel-coated stent (Zilver PTX) after the treating physician had successfully crossed the target lesion with a guidewire. Randomisation to treatment was stratified by study site and was done with a site-specific, web-based randomisation schedule, with random permuted blocks of varying sizes. For the randomised study, a patient was considered enrolled when their treatment assignment was received by the study site. For the pharmacokinetic substudy, enrolment occurred when the Eluvia stent was introduced into the patient's vasculature.

Patients remained masked to the treatment assigned and received until all patients had completed the follow-up visit at 12 months. The Clinical Events Committee, site personnel who did clinical follow-up assessments (except when done by the implanting investigator), core laboratory personnel (who assessed duplex ultrasonography and angiography), and individuals involved in the data analysis were also masked to treatment assignment until the primary endpoint analysis. An independent data reviewer, masked to treatment assignment, monitored aggregate safety data. The sponsor did not have access to treatment assignment and a third-party contract research organisation performed the statistical analysis.

Procedures

The Eluvia Vascular Stent System is a self-expanding stent made of a nickel titanium alloy (nitinol). The stent delivery system and nitinol platform are the same as the Innova self-expanding stent (Boston Scientific, Marlborough, MA, USA), which is purpose built for use in the superficial femoral or proximal popliteal arteries. The Eluvia stent is coated with a primer polymer of poly(n-butyl methacrylate) and an active layer composed of matrix polymer poly(vinylidene fluoride-co-hexafluoropropylene) and paclitaxel at a dose density of 0·167 μg paclitaxel per mm² stent surface area. These polymers are the same as those on the Xience V (Abbot Vascular, Abbott Park, IL, USA) and Promus Element and Promus Element Plus (Boston Scientific, Marlborough, MA, USA) coronary stents and thus have well documented safety profiles from long-term investigation in coronary applications.[13,14]

The control stent was the commercially available Zilver PTX Stent System, which is a self-expanding nitinol stent with a polymer-free paclitaxel coating (3 μg/mm²). Stent lengths and diameters available for use in the study are shown in the appendix.

Anticoagulation and antiplatelet therapy administered during the procedure were consistent with current clinical practice. At a minimum, clopidogrel 75 mg or ticlopidine started at least 24 h before the procedure or a peri-procedural loading dose (recommended loading dose of clopidogrel 300 mg or ticlopidine 200 mg) was given. Dual antiplatelet therapy was required for the first 60 days after the procedure, in accordance with previous trials of both devices.[15,16] Antiplatelet monotherapy was required throughout the 12 months of follow-up and recommended through trial completion at 5 years.

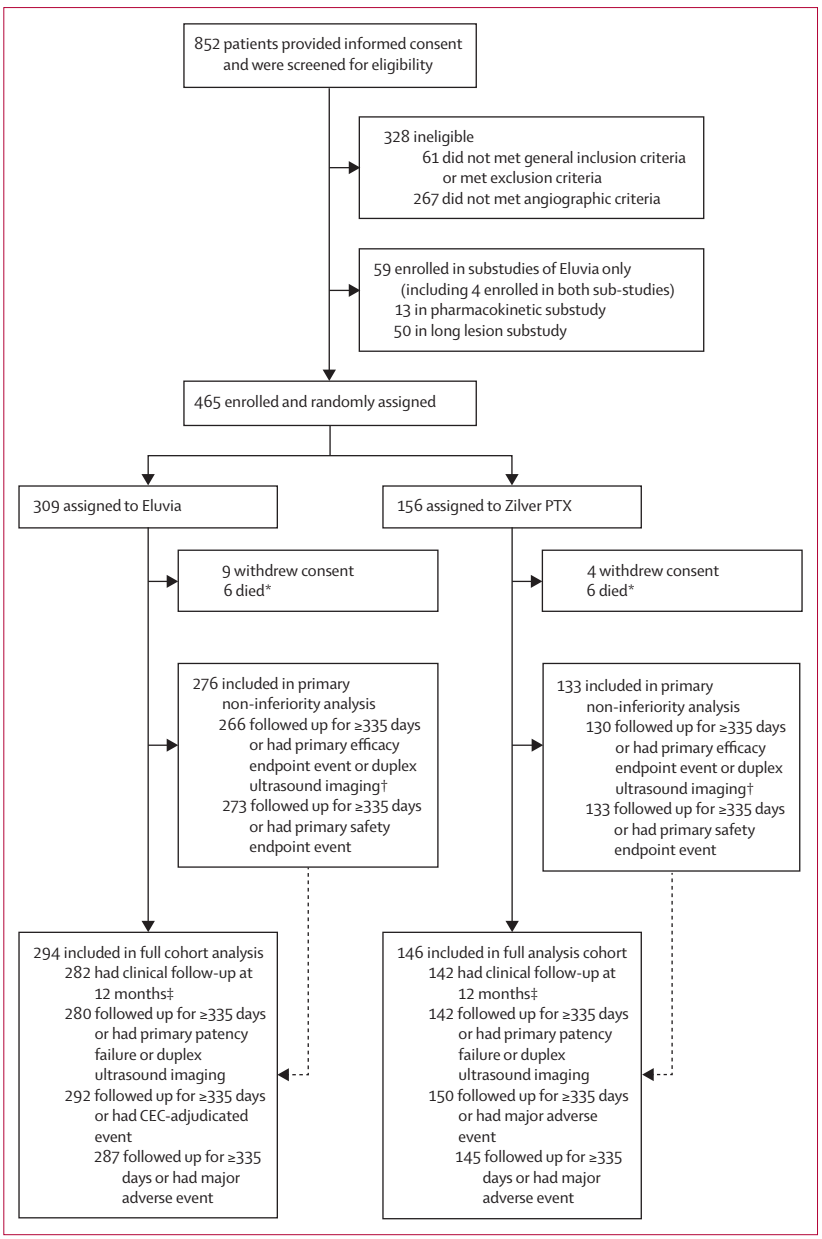

Figure 1: **Trial profile**
CEC=Clinical Events Committee. *Patients who died were included in the full analysis cohort for CEC-adjudicated events. †Primary non-inferiority analyses were done when the minimum number of intention-to-treat patients required for 80% power had completed the 12-month follow up with evaluable duplex ultrasound or primary patency failure. ‡Clinical outcome analytic set. Complete assessment data were required for the patient to be included in the analysis of a specific outcome.

Clinical follow-up visits related to the study were scheduled for 1 month, 6 months, and 12 months after the procedure, with follow-up planned to continue through 5 years, including clinical visits at 24 months and 5 years and clinical or telephone follow-up at 3 and 4 years.

For the pharmacokinetic substudy, patients had venous blood drawn before stent implantation, at 10 min, 30 min, and 1 h, 2 h, 3 h, 4 h, 6 h, 12, and 24 h after implantation, and then at either 48 h or 72 h after implantation. Plasma

	Eluvia (n=309)	Zilver PTX (n=156)
Age (years)	68·5 (9·5)	67·8 (9·4)
Sex		
Male	204/309 (66%)	104/156 (67%)
Female	105/309 (34%)	52/156 (33%)
Race or ethnicity		
Hispanic or Latino	18/309 (6%)	6/156 (4%)
White	205/309 (66%)	108/156 (69%)
Asian	57/309 (18%)	28/156 (18%)
Japanese	56/309 (18%)	28/156 (18%)
Black or African American	21/309 (7%)	11/156 (7%)
Native Hawaiian or other Pacific Islander	1/309 (<1%)	0
American Indian or Alaska Native	2/309 (1%)	2/156 (1%)
Other	3/309 (1%)	1/156 (1%)
Not disclosed	2/309 (1%)	0
Smoking status		
Current	109/309 (35%)	63/156 (40%)
Previous	157/309 (51%)	68/156 (44%)
Never	42/309 (14%)	22/156 (14%)
Unknown	1/309 (<1%)	3/156 (2%)
Diabetes	129/309 (42%)	68/156 (44%)
Type 1	3/129 (2%)	3/68 (4%)
Type 2	119/129 (92%)	64/68 (94%)
Unknown	7/129 (5%)	1/68 (1%)
Medically treated	116/129 (90%)	64/68 (94%)
Oral drug	93/129 (72%)	51/68 (75%)
Insulin	49/129 (38%)	26/68 (38%)
Other	2/129 (2%)	0
Unknown	1/129 (1%)	1/68 (1%)
Hyperlipidaemia	235/308 (76%)	118/156 (76%)
Hypertension	254/309 (82%)	133/156 (85%)
Coronary artery disease	156/307 (51%)	70/155 (45%)
Myocardial infarction	60/306 (20%)	27/154 (18%)
Congestive heart failure	26/307 (8%)	12/154 (8%)
Renal insufficiency	25/309 (8%)	11/156 (7%)

Data are mean (SD) or n/N (%).

Table 1: **Baseline demographic and clinical characteristics of the intention-to-treat population**

	Eluvia (n=309)	Zilver PTX (n=156)
Treated limb		
Right leg	159/309 (51%)	86/156 (55%)
Left leg	150/309 (49%)	70/156 (45%)
Arterial segment*		
Ostial	5/309 (2%)	1/156 (1%)
Proximal superficial femoral artery	40/309 (13%)	16/156 (10%)
Mid superficial femoral artery	201/309 (65%)	104/156 (67%)
Distal	205/309 (66%)	102/156 (65%)
Proximal popliteal artery	37/205 (18%)	13/102 (13%)
Lesion length (mm)	86·5 (36·9; n=308)	81·8 (37·3; n=154)
Lesion type		
Eccentric	206/308 (67%)	104/155 (67%)
Concentric	102/308 (33%)	51/155 (33%)
Thrombus grade 0	308/308 (100%)	155/155 (100%)
Calcification		
None or mild	112/307 (36%)	50/155 (32%)
Moderate	70/307 (23%)	54/155 (35%)
Severe	123/307 (40%)	50/155 (32%)
Unknown	2/307 (1%)	1/155 (1%)
Ulceration	16/309 (5%)	4/156 (3%)
Aneurysm	0	4/156 (3%)
Patency to foot	293/309 (95%)	146/156 (94%)
Anterior tibial artery (patent)	130/309 (42%)	74/156 (47%)
Posterior tibial artery	179/309 (58%)	95/156 (61%)
Peroneal artery	221/309 (72%)	101/156 (65%)
Profunda femoris artery	257/309 (83%)	129/156 (83%)
Percent diameter stenosis	80·7% (16·5%; n=308)	80·8% (16·4%; n=155)
<50%	5/308 (2%)	3/155 (2%)
50–99%	207/308 (67%)	105/155 (68%)
100% (occlusion)	96/308 (31%)	47/155 (30%)

Data are mean (SD; number of patients) or n/N (%), unless otherwise stated. *More than one arterial segment per patient was allowed.

Table 2: **Baseline angiographic characteristics**

paclitaxel concentrations were quantified by high-performance liquid chromatography followed by tandem mass spectrometry (Covance Laboratories, Madison, WI, USA).

At 12 months after stent implantation, plain-film radiographs were obtained to assess stent integrity. Radiographs were assessed by an independent core laboratory (VasCore, Boston, MA, USA), and possible fractures were verified by comparison with procedural angiography by the angiographic core lab (Beth Israel Deaconess Medical Center, Boston, MA, USA) and graded (grade 0, no strut fractures; grade 1, single strut fracture; grade 2, multiple strut fractures; grade 3, stent fracture with preserved alignment of the components; grade 4, stent fracture with malalignment of the components; grade 5, stent fracture in a trans-axial spiral configuration).[17]

Outcomes

The primary efficacy endpoint of the randomised controlled trial was primary vessel patency at 12 months, which was defined as a binary endpoint based on a duplex ultrasound peak systolic velocity ratio of 2·4 or lower at the 12-month follow-up visit as assessed by the duplex ultrasound core laboratory (VasCore), in the absence of clinically driven target lesion revascularisation or bypass of

	Eluvia (n=309)	Zilver PTX (n=156)	Difference (95% CI)	p value
Primary outcomes				
Primary patency*	86·8% (243/280)	77·5% (110/142)	9·3% (1·4 to 17·3)	0·0144
Major adverse events†	4·9% (14/287)	9·0% (13/145)	−4·1% (−9·4 to 1·2)	0·098
Any death at 1 month	0% (0/287)	0% (0/145)	0	NA
Major amputation of target limb	0·3% (1/287)	0% (0/145)	0·3% (−0·3 to 1·0)	1·00
Clinically driven target lesion revascularisation	4·5% (13/287)	9·0% (13/145)	−4·4% (−9·7 to 0·8)	0·067
Secondary outcomes				
CEC-adjudicated events				
Any death	2·1% (6/292)	4·0% (6/150)	−1·9% (−5·5 to 1·6)	0·23
Target lesion revascularization	4·5% (13/292)	8·7% (13/150)	-4·2% (-9·3%, 0·9%)	0·0746
Target vessel revascularisation	6·8% (20/292)	8·7% (13/150)	−1·8% (−7·2 to 3·5)	0·49
Target limb amputation	0·3% (1/292)	1·3% (2/150)	-1·0% (-2·9%, 1·0%)	0·2668
Stent thrombosis	1·7% (5/292)	4·0% (6/150)	-2·3% (-5·8%, 1·2%)	0·1956
Clinical Outcomes				
Primary sustained clinical improvement‡	89·6% (250/279)	83·1% (118/142)	6·5% (−0·6 to 13·6)	0·057
Haemodynamic improvement§	80·8% (223/276)	78·7% (111/141)	2·1% (−6·1 to 10·3)	0·62
Walking impairment questionnaire scores¶	40·8 (36·5)	35·8 (39·5)	5·0 (−2·6 to 12·6)	0·20
Distance	33·2 (38·3)	29·5 (38·2)	3·7 (−4·1 to 11·4)	0·35
Speed	18·3 (29·5)	18·1 (28·7)	0·2 (−5·8 to 6·1)	0·96
Stair climbing	19·4 (36·7)	21·1 (34·6)	−1·7 (−9·0 to 5·6)	0·65
6-min walk test¶				
Distance (m)	44·5 (119·5)	51·8 (130·5)	−7·3 (−33·5 to 18·8)	0·58
Speed (m/min)	5·4 (18·7)	7·9 (20·3)	−2·6 (−6·6 to 1·5)	0·22

Data are percentage (n/N) or mean (SD). NA=not appropriate. The mean number of stents received was 1·0 (SD 0·18) in the Eluvia group and 1·3 (0·45) in the Zilver PTX group. Analysis for each outcome required complete assessment data. *Defined as a duplex ultrasound peak systolic velocity ratio ≤2·4 at the 12-month follow-up visit, in the absence of clinically driven target lesion revascularisation or bypass of the target lesion. The superiority analysis of primary patency in the full-analysis cohort was a prespecified post-hoc analysis. †All causes of death through 1 month and target limb major amputation or target lesion revascularisation through 12 months are shown. ‡Defined as improvement in Rutherford classification by one or more categories compared with baseline, without target lesion revascularisation. §Defined as an increase in the ankle-brachial index by ≥0·10 compared with baseline or to an ankle-brachial index ≥0·90, without target lesion revascularisation. ¶Change from baseline shown.

Table 3: **Clinical outcomes at 12 months after stent implantation in the full-analysis cohort**

the target lesion. Clinically driven target lesion revascularisation was defined as a re-intervention within 5 mm proximal or distal to the original treatment segment for 50% or higher angiographic diameter stenosis in the presence of recurrent symptoms (increase in Rutherford category of 1 or more) or associated with a decrease in the ankle-brachial index of 20% or more (or ≥0·15) in the treated segment (tibial brachial index was allowed in cases of incompressible vessels). The primary safety endpoint was the occurrence of major adverse events, defined as all causes of death through 1 month, major amputation of the target limb through 12 months, or target lesion revascularisation through 12 months. The Clinical Events Committee adjudicated all major adverse events.

Secondary endpoints at 12 months were technical success (defined as deployment of the assigned study stent to the target lesion to achieve residual angiographic stenosis ≤30% when assessed visually), procedural success (defined as technical success with no major adverse events within 24 h of the index procedure), adverse events, stent integrity, Clinical Events Committee-adjudicated events that did not meet the definition for major adverse events (any death, target lesion revascularisation, any target limb amputation, and stent thrombosis), and clinical outcomes. Clinical outcomes were distribution of Rutherford category, primary sustained clinical improvement (assessed with Rutherford categorisation), haemodynamic improvement (assessed with the ankle-brachial index), and walking function (assessed with the Walking Impairment Questionnaire, the 6-min walk test, and the health-related quality of life EQ-5D questionnaire). Secondary endpoints also included the Rutherford categorisation, Walking Impairment Questionnaire, and EQ-5D assessments at 1 month and 6 months post-procedure. Plasma paclitaxel concentrations were the primary endpoint for the pharmacokinetic substudy.

Statistical analysis

The overall sample size in the randomised trial was selected to preserve adequate statistical power for non-inferiority testing of the primary efficacy and safety endpoints at a prespecified, one-sided significance level of 5% for each, without adjustment for multiplicity. For this trial to be deemed a success, both the primary efficacy endpoint and the primary safety endpoint had to be met (ie, they were coprimary endpoints).

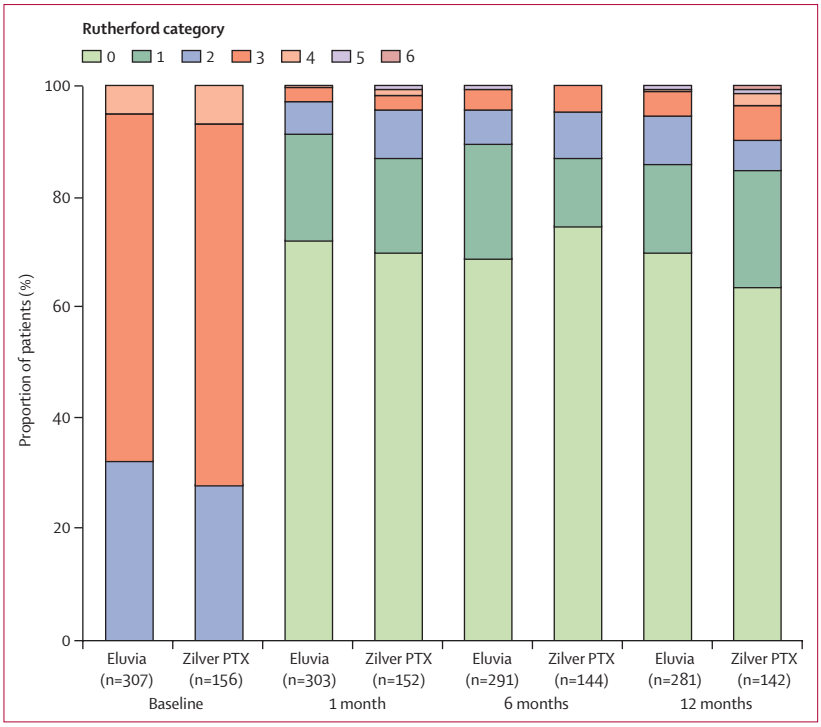

Figure 2: **Distribution of Rutherford categories in the full-analysis set**

To retain a minimum of 393 evaluable patients (ie, at least 80% power) for the primary efficacy analysis, we planned to randomly assign a maximum of 465 patients in a 2:1 manner (ideally 310 to the Eluvia group and 155 to the Zilver PTX group). The assumptions for sample size calculation included a 15% attrition rate, 83% primary patency for Zilver PTX,[15] a one-sided type I error of 5%, and a –10% non-inferiority margin. This non-inferiority margin allowed the observed primary patency rate for the Eluvia group to be less than that of the Zilver PTX group by only 3% for the non-inferiority efficacy endpoint to be met. We established that a difference of 3 percentage points was clinically meaningful by expert consensus because efficacy data for paclitaxel-eluting stents in the femoropopliteal segment were limited to a single randomised trial[15] at the time the study was designed. In view of the expected event rates for the primary safety endpoint, a –10% non-inferiority margin meant the lower limit of the 95% CI would be greater than the non-inferiority margin only if the difference in observed rates was no more than 4 percentage points. The pharmacokinetic substudy was observational, and the sample size for that study was established per agreement with the US Food and Drug Administration.

The primary non-inferiority analyses were done when the minimum number of patients required for 80% statistical power had evaluable efficacy results. Thus, the primary efficacy non-inferiority analysis included a minimum-sized initial sample (about 85% of all enrolled study patients) of patients who completed 12 months of follow-up who had evaluable ultrasound images or primary patency failure. The primary safety non-inferiority analysis included all patients who had completed 12 months of follow-up at the time the adequate efficacy analysis sample size was reached, or had a major adverse event. The non-inferiority analyses were also done on the per-protocol sample within this initial analytical set, which included only randomised patients who received the assigned treatment.

A non-inferiority test, such as the Farrington-Manning method, was used to estimate the lower bound for the 95% CI of the difference between treatment groups (Eluvia minus Zilver PTX). If this lower bound was greater than the non-inferiority margin of –10%, Eluvia would be considered non-inferior to Zilver PTX in terms of device efficacy. The same testing procedure was simultaneously (ie, no hierarchical testing) done for device safety.

All other reported analyses, including those of secondary endpoints and a post-hoc superiority analysis, were done after the 12-month follow-up window for all enrolled patients had passed, and so included the full cohort of patients who had a minimum of 12 months of follow-up, a previous endpoint event, or a 12-month clinical visit, as required for each assessment. The superiority analysis for primary patency included all patients who completed 12 months of follow-up with evaluable duplex radiographs or had primary patency failure before the end of the 12-month visit window. To avoid multiplicity, the success criteria for superiority could only be implemented if Eluvia was shown to be non-inferior to Zilver PTX. For the full cohort, two-sided 95% CIs were calculated for the difference between groups in observed primary patency rates. Adverse events were also assessed for all patients.

Categorical variables are reported as counts and percentages and compared with χ^2 tests. Continuous variables are reported as mean (SD) and compared with paired t tests. The Kaplan-Meier product-limit method was used to estimate time to primary patency failure and target lesion revascularisation in the full-analysis set. Patients without an event at 13 months of follow-up or later were censored at 13 months. Treatment groups were compared with log-rank tests. A p value of less than 0·05 indicated a significant difference.

Statistical analyses were done with SAS, version 9.2 or higher.

This trial is registered with ClinicalTrials.gov, number NCT02574481.

Role of the funding source

The funder of the study was involved in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author and the senior author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 2, 2015, and Feb 15, 2017, 852 patients were screened for eligibility and 465 were randomly assigned to Eluvia (n=309) or to Zilver PTX (n=156; figure 1). The assigned device was implanted in 462 patients (two patients assigned to Zilver PTX received an Eluvia stent and one patient assigned to Eluvia received a Zilver PTX stent). 424 patients completed a 12-month follow-up visit. 12 patients (six in each group) died before 12 months from cardiac (three in the Eluvia group and five in the Zilver PTX group), vascular (one in the Zilver PTX group, not considered by the site investigator to be related to the study device), or non-cardiovascular (three in the Eluvia group) causes.

Baseline demographic, clinical, and angiographic characteristics were similar between the two study groups (tables 1, 2). Predilation with a balloon was done in 273 (88%) of 309 patients in the Eluvia group and in 132 (85%) of 156 patients in the Zilver PTX group. Residual angiographic stenosis of no greater than 30% (defined as technical success) was reported for 308 patients in the Eluvia group and all 156 patients in the Zilver PTX group; the one site-reported technical failure was not confirmed as technical failure by the angiographic core laboratory. No major adverse events were reported within 24 h of the procedure. Aspirin use was reported for 292 (94%) patients in the Eluvia group and 148 (95%) patients in the Zilver PTX group at discharge and in 246 (88%) patients in the Eluvia group and 128 (90%) patients in the Zilver PTX group at 12 months. Dual antiplatelet therapy was reported for 287 (93%) patients in the Eluvia group and 144 (93%) patients in the Zilver PTX group at discharge and in 167 (60%) patients in the Eluvia group and 86 (61%) patients in the Zilver PTX group at 12 months.

The primary non-inferiority analyses were done when 409 patients (276 in the Eluvia group and 133 in the Zilver PTX group) had completed 12 months of follow-up or had a primary efficacy or safety endpoint event (figure 1). Non-inferiority was shown for both efficacy and safety endpoints at 12 months. Primary patency was observed for 231 (87%) of 266 patients in the Eluvia group and for 106 (82%) of 130 patients in the Zilver PTX stent group (difference 5·3% [one-sided lower bound of 95% CI –0·66]; p<0·0001). 259 (95%) of 273 patients in the Eluvia group and 121 (91%) of 133 patients in the Zilver PTX group had not had a major adverse event at 12 months (difference 3·9% [onse-sided lower bound of 95% CI –0·46]; p<0·0001). Analysis of the per-protocol patients within this initial cohort yielded similar results (appendix).

Secondary endpoints improved after stent implantation and were generally similar between the groups (table 3). At 12 months, of the patients with complete Rutherford assessment data, 241 (86%) of 281 patients in the Eluvia group and 120 (85%) of 142 patients in the Zilver PTX group had symptoms reported as Rutherford category 0 or 1 (none to mild claudication; figure 2). The mean ankle-brachial index was 1·0 (SD 0·2) in both groups at 12 months (baseline mean ankle-brachial index 0·7 [SD 0·2] for Eluvia; 0·8 [0·2] for Zilver PTX), with sustained

	Baseline	1 month	6 months	12 months
Eluvia (n=309)				
Walking impairment	37·8 (29·2)	82·2 (26·3)	81·9 (26·6)	79·1 (29·1)
Change from baseline	..	44·1 (33·4)	43·4 (34·5)	40·8 (36·5)
p value	..	<0·0001	<0·0001	<0·0001
Distance scores	30·8 (30·8)	69·1 (36·9)	67·1 (38·4)	64·6 (37·8)
Change from baseline	..	38·1 (36·8)	35·6 (37·1)	33·2 (38·3)
p value	..	<0·0001	<0·0001	<0·0001
Speed scores	24·6 (21·8)	45·6 (29·4)	45·5 (29·2)	43·7 (29·1)
Change from baseline	..	20·7 (28·1)	20·2 (28·4)	18·3 (29·5)
p value	..	<0·0001	<0·0001	<0·0001
Stair climbing scores	40·9 (32·7)	63·7 (35·4)	64·9 (35·8)	61·0 (34·8)
Change from baseline	..	22·8 (34·3)	23·6 (36·0)	19·4 (36·7)
p value	..	<0·0001	<0·0001	<0·0001
Zilver PTX (n=156)				
Walking impairment	41·1 (28·2)	82·4 (27·0)	79·2 (29·7)	77·8 (31·24)
Change from baseline	..	41·3 (37·3)	37·0 (38·1)	35·8 (39·5)
p value	..	<0·0001	<0·0001	<0·0001
Distance scores	32·2 (30·6)	65·0 (36·9)	66·0 (37·7)	63·4 (38·1)
Change from baseline	..	32·7 (36·9)	32·5 (36·3)	29·5 (38·2)
p value	..	<0·0001	<0·0001	<0·0001
Speed scores	24·6 (20·0)	44·0 (28·1)	44·6 (29·2)	43·7 (29·4)
Change from baseline	..	19·3 (28·2)	19·3 (28·1)	18·1 (28·7)
p value	..	<0·0001	<0·0001	<0·0001
Stair climbing scores	38·0 (32·8)	61·5 (36·4)	62·2 (37·3)	59·8 (38·6)
Change from baseline	..	23·4 (35·7)	23·0 (36·9)	21·1 (34·6)
p value	..	<0·0001	<0·0001	<0·0001

Data are mean (SD). Analysis for each outcome required complete assessment data. Data was available for 306 patients at baseline, 305 patients at 1 month, 292 patients at 6 months and 282 patients at 12 months in the Eluvia group. Data was available for 155 patients at baseline, 154 patients at 1 month, 145 patients at 6 months, and 142 patients at 12 months in the Zilver PTX group.

Table 4: **Walking impairment questionnaire results**

	Baseline	12 months
Eluvia (n=309)		
Total walk time (min)	5·4 (1·2)	5·7 (0·9)
Total distance walked (m)	271·9 (135·4)	323·8 (148·5)
Speed (m/min)*	49·0 (20·2)	55·5 (23·3)
Zilver PTX (n=156)		
Total walk time (min)	5·5 (1·2)	5·6 (1·0)
Total distance walked (m)	267·4 (132·8)	323·4 (155·4)
Speed (m/min)*	47·8 (20·5)	56·1 (24·1)

Data are mean (SD). Data was available for 293 patients at baseline and 269 patients at 12 months in the Eluvia group. Data was available for 145 patients at baseline and 136 patients at 12 months in the Zilver PTX group. Four patients had more than 6 min total walking time. *p<0·0001 for the difference in speed between baseline and 12 months.

Table 5: **6-min walk test results**

	Eluvia (n=309)	Zilver PTX (n=156)	Difference (95% CI)	p value
Baseline to 1 month				
Mobility	66·0% (200/303)	63·4% (97/153)	2·6% (–6·7 to 11·9)	0·58
Self-care	6·6% (20/303)	6·5% (10/153)	0·1% (–4·7 to 4·9)	0·98
Usual activities	39·6% (120/303)	31·4% (48/153)	8·2% (–1·0 to 17·4)	0·085
Pain or discomfort	53·1% (161/303)	55·6% (85/153)	–2·4% (–12·1 to 7·3)	0·62
Anxiety or depression	20·1% (61/303)	18·3% (28/153)	1·8% (–5·8 to 9·4)	0·64
Baseline to 6 months				
Mobility	66·2% (192/290)	57·3% (82/143)	8·9% (–0·9 to 18·6)	0·072
Self-care	6·6% (19/290)	7·0% (10/143)	–0·4% (–5·5 to 4·6)	0·86
Usual activities	41·0% (119/290)	34·3% (49/143)	6·8% (–2·9 to 16·4)	0·17
Pain or discomfort	50·7% (147/290)	51·0% (73/143)	–0·4% (–10·4 to 9·7)	0·94
Anxiety or depression	16·9% (49/290)	21·7% (31/143)	–4·8% (–12·8 to 3·2)	0·23
Baseline to 12 months				
Mobility	60·2% (168/279)	52·1% (74/142)	8·1% (–1·9 to 18·1)	0·11
Self-care	6·5% (18/279)	7·0% (10/142)	–0·6% (–5·7 to 4·5)	0·82
Usual activities	39·8% (111/279)	35·2% (50/142)	4·6% (–5·2 to 14·3)	0·36
Pain or discomfort	49·8% (139/279)	46·5% (66/142)	3·3% (–6·7 to 13·4)	0·52
Anxiety or depression	18·6% (52/279)	16·9% (24/142)	1·7% (–5·9 to 9·4)	0·66

Improvement was defined as improvement of at least one level from baseline within the dimension (level of problems in each dimension ranked as none, slight, moderate, severe, extreme). Analysis for each outcome required complete assessment data. Percentage differences were calculated to two significant figures and rounded. Data were available for 303 patients at 1 month, 290 patients at 6 months, and 279 patients at 12 months in the Eluvia group. Data were available for 153 patients at 1 month, 143 patients at 6 months, and 142 patients at 12 months in the Zilver PTX group.

Table 6: **Improvement in health-related quality of life (EQ-5D)**

haemodynamic improvement for about 80% of patients in both groups (table 3). Walking function improved significantly from baseline to 12 months in both groups, as measured with the Walking Impairment Questionnaire (table 4) and the 6-min walk test (table 5). In both groups, the majority of patients had sustained improvement in the mobility dimension of the EQ-5D and roughly half had sustained improvement in the pain or discomfort dimension (table 6). No significant between-group differences were observed in the Walking Impairment Questionnaire, 6-min walk test, or EQ-5D, although the proportion of patients with clinically driven target lesion revascularisation in the Zilver PTX group was twice that in the Eluvia group at 1 year (table 3). The distributions of responses across the EQ-5D dimensions are in the appendix. Hospital readmissions related to re-interventions were reported for 12 (4%) of 309 patients in the Eluvia group and 11 (7%) of 156 patients in the Zilver PTX group through 12 months (appendix).

Superiority was met in the post-hoc analysis of 12-month primary patency in the full-analysis cohort (difference 9·3% [95% CI 1·4–17·3]; table 3). The proportion of patients in the full-analysis cohort who had had a major adverse event at 12 months did not differ significantly between the groups, and most major adverse events were clinically driven target lesion revascularisations (table 3). All target lesion re-vascularisations were considered to be clinically driven according to prespecified criteria. Kaplan-Meier estimates of primary patency and target lesion revascularisation were consistent with the observed rates for the full-analysis cohort (figure 3).

Of the patients with 12 month follow-up or a Clinical Events Committee-adjudicated event, one (0·3%) of 292 patients in the Eluvia group and two (1·3%) of 150 patients in the Zilver PTX group had any target limb amputation at 12 months (difference –1·0% [95% CI –2·9 to 1·0]; p=0·27; table 3). The proportion of patients who had stent thrombosis was low (1·7% [5/292] in the Eluvia group and 4·0% [6/150] in the Zilver PTX group) and did not differ significantly between the groups (difference –2·3% [95% CI –5·8 to 1·2]; p=0·20; table 3). One of 319 implanted Eluvia stents had grade 3 stent fracture (Eluvia 150 mm length) identified via radiography and verified by comparison with angiographic images. The patient's vessel was patent and they had no major adverse events at 12 months of follow-up. No fractures were identified in the Zilver PTX group.

No unanticipated adverse events were reported, and adverse events were similar between the study groups through 12 months (appendix). Serious adverse events were reported in 128 (41%) of 309 patients in the Eluvia group and in 66 (42%) of 156 patients in the Zilver PTX group, device-related adverse events in 25 (8%) patients in the Eluvia group and in 22 (14%) patients in the Zilver PTX group, and procedure-related adverse events in 59 (19%) patients in the Eluvia group and 27 (17%) patients in the Zilver PTX group. No aneurysmal degeneration of stented lesions was reported during the 12 months of follow-up; however, after some cases observed in a registry in Germany were reported,[18] personnel at the core laboratory reviewed all available and suitable 1-year duplex ultrasound images and found six cases (all in the Eluvia group). Five of those patients had chronic occlusions at baseline. All six patients were patent at 1 year and none had experienced target lesion revascularisation or stent thrombosis.

In the pharmacokinetic substudy, plasma paclitaxel concentrations were less than 1·00 ng/mL for all but two patients at all measured timepoints; at 10 min after implantation, two patients had slightly higher concentrations (1·60 ng/mL and 1·44 ng/mL), which decreased to less than 1·00 ng/mL at 30 min post-procedure.

Discussion

The algorithm for endovascular intervention for lower-extremity atherosclerotic peripheral artery disease is poorly defined. Early practice guidelines suggested endovascular treatment for short lesions (<10 cm),[19,20] and stent implantation was recognised as a salvage option.[20] European Society of Cardiology guidelines published in 2017, included endovascular treatment as an option for

lesions up to 25 cm and recognised the potential benefit of primary stent implantation and drug-eluting devices,[21] but recommendations to date have been limited by the absence of evidence from randomised trials.[21] In this head-to-head randomised trial, the primary non-inferiority endpoints for efficacy and safety at 12 months were met, and post-hoc analysis of the 12-month patency rate showed superiority for Eluvia over Zilver PTX. The proportions of patients with stent thrombosis or clinically driven target lesion revascularisation in the Eluvia stent group were about half those in the Zilver PTX group. Both groups showed improvements in clinical symptoms and walking function and the occurrence of stent fracture was low. The pharmacokinetics substudy confirmed that plasma paclitaxel concentrations after Eluvia implantation were well below thresholds associated with toxic effects in studies in patients with cancer (0·05 µM or ~43 ng/mL).[22] Transverse ultrasound images, which provide the best view for diagnosis of aneurysmal degeneration of the wall or excessive positive remodelling in the form of a hypoechoic halo surrounding the stent, were unfortunately not available for all patients. Appropriate duplex ultrasound images will be collected during subsequent follow-up visits to establish a more definitive rate of aneurysmal degeneration and observe evolution.

Although variation in patient and lesion characteristics must be considered, the results for both stents are consistent with results from previous studies. Baseline clinical characteristics of the patients treated with Eluvia in this study were similar to those of patients included in the MAJESTIC first-in-human study,[16] with the mean lesion length less than 10 cm in both studies. The primary patency rate at 1 year was greater in MAJESTIC (96·4%) than in this study, although the safety profiles were similar. Patient characteristics in an all-comer registry[18] were more complex than in this study, with a mean lesion length of 200 mm, 79% of patients with occlusions, and nearly half with critical limb ischaemia. Despite this complexity, the patency rate observed at 1 year for patients treated with Eluvia was 87%, which was similar to that observed in this trial. Similarly, the characteristics of patients treated with Zilver PTX in an earlier randomised controlled trial[15] and a single-arm study[23] were generally similar to patients treated with Zilver PTX in this study, with mean lesion lengths of less than 10 cm in all studies. The reported 12-month patency rates range from 77·5% to 86·0% in these three studies. Among patients with longer lesions (mean length 147–252 mm) treated with Zilver PTX as summarised by Bisdas and colleagues,[18] 1-year primary patency rates ranged from 56% to 86%.

The benchmark for endovascular treatment durability (ie, maintaining vessel patency) in the superficial femoral artery was initially set by standard percutaneous transluminal angioplasty in the 2000s.[17] Drug-eluting technologies have since raised expectations for endovascular treatment of femoropopliteal disease,[4–7,11,15] making comparisons with standard percutaneous transluminal angioplasty or bare-metal stents non-informative. IMPERIAL was designed to compare two drug-eluting stents because scaffolding is more commonly used to treat lesions with certain characteristics (eg, long lesion length or severe calcification). The Zilver PTX stent was chosen as the control device because it is the only commercially available, self-expanding, nitinol, drug-coated stent approved for the treatment of superficial femoral artery and proximal popliteal artery lesions. Although both Eluvia and Zilver PTX include paclitaxel, the drug concentrations and elution profiles of the two stents differ, with the rapid drug delivery profile of Zilver PTX similar to that of a drug-coated balloon.[24]

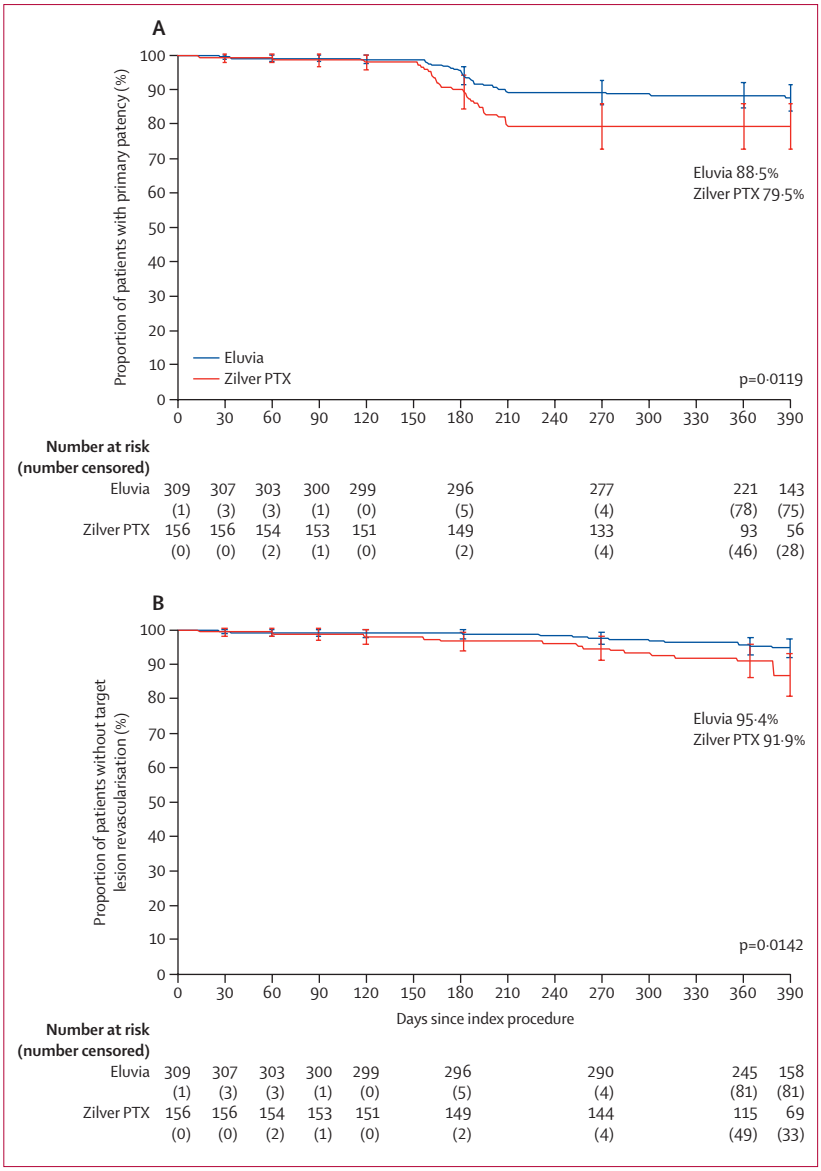

Figure 3: **Time to primary patency failure (A) and target lesion revascularisation (B) in the full-analysis cohort**
Bars show 95% CI. Differences between groups were assessed with the log-rank test.

For the **Boston Scientific Data Sharing Policy** see http://www.bostonscientific.com/en-US/data-sharing-requests.html

Efficacy outcomes observed in the early SIROCCO[25] and STRIDES[26] studies of drug-eluting stents (sirolimus and everolimus, respectively) in the peripheral vasculature were disappointing, and possible explanations for the results included too-short elution duration and potential polymer bioincompatibility. The longer elution period for Eluvia compared with Zilver PTX might contribute to Eluvia's superior efficacy in this trial. Given that sustained drug elution depends on the presence of a polymer, the similarly low complication rates in patients treated with either stent in this study, together with the documented safety profile of the polymer coating used on Eluvia,[13,14] support the biocompatibility of the Eluvia coating.

Strengths of the IMPERIAL study include randomised treatment assignment with a contemporary comparator and masking of individuals at core laboratories. The study did not include an assessment of masking success. Medical records were not masked, and ascertainment bias is possible for some variables because surgeons could not be masked to treatment assignment. The patient characteristics were clinically relevant, with representative proportions of patients with diabetes, occlusions, and severe calcification, although the generalisability of the results to patients with longer lesions might be limited. Assumptions included in the study design, such as the clinical meaning of the –10% non-inferiority margin (which corresponds to a 3% difference in observed primary patency rate), are also limitations because they were based on expert opinion. However, the observed patency rates were similar to the assumed rates used in the sample size calculation, supporting the validity of the analyses. The 12-month follow-up period reported here is clinically relevant, but longer-term outcomes are important,[9,11] and follow-up will continue through 5 years.

In conclusion, we showed that a paclitaxel-eluting, polymer-coated stent was non-inferior to a paclitaxel-coated, polymer-free stent in maintaining primary patency at 12 months, and had a similar safety profile. Based on these results, the use of a polymer-coated paclitaxel-eluting stent in patients who require superficial femoral artery or popliteal intervention is a reasonable approach to maximise intermediate-term patency and to maintain haemodynamic and clinical improvement without repeat re-intervention.

Contributors

WAG, SM-H, and JD-C designed the study and wrote the manuscript. WAG, KK, YS, ABe, ABa, YY, HS, JTP, AH, and SM-H participated in data collection. WAG, SM-H, JD-C, JP, and MRJ participated in data analysis. All authors contributed to data interpretation.

Declaration of interests

WAG, YS, YY, JTP, and AH serve as advisors to Boston Scientific. ABe reports receiving research funding from Medtronic and Soundbite Medical, is a shareholder in Soundbite Medical, and has received speaking fees from Medtronic, Cordis, and Boston Scientific. ABa reports receiving honoraria for physician training from Boston Scientific, Abbott Vascular, Medtronic, and Cook. JP reports grants from Boston Scientific, Medtronic, Abbott Vascular, Cook, and Terumo; personal fees from Boston Scientific (medical advisory board, educational course); and grants and personal fees from Edwards Lifesciences. MRJ serves as a non-compensated advisor to Boston Scientific, Abbott Vascular, Cordis, a Cardinal Health Company, and Medtronic, and reports personal fees from Philips Volcano, consultant equity from Micell and Vactronix, and investments in Vascular Therapies, Vactronix Scientific, and Gemini. JD-C is an employee of, and owns stock in, Boston Scientific. SM-H serves as a consultant for, and has received honoraria and travel grants from, Boston Scientific, and has received personal fees from Terumo. KK and HS declare no competing interests.

Data sharing

The data and study protocol for this clinical trial might be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy.

Acknowledgments

IMPERIAL was funded by Boston Scientific. We thank H Terry Liao (Boston Scientific) for designing the statistical analysis plan and Elizabeth J Davis (Boston Scientific) for providing medical writing assistance.

References

1 Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res* 2015; **116:** 1509–26.

2 Murphy TP, Cutlip DE, Regensteiner JG, et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. *J Am Coll Cardiol* 2015; **65:** 999–1009.

3 Egorova NN, Guillerme S, Gelijns A, et al. An analysis of the outcomes of a decade of experience with lower extremity revascularization including limb salvage, lengths of stay, and safety. *J Vasc Surg* 2010; **51:** 878–85.

4 Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and/or popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. *Circulation* 2015; **131:** 495–502.

5 Krishnan P, Faries P, Niazi K, et al. Stellarex Drug-coated balloon for treatment of femoropopliteal disease: 12-month outcomes from the randomized ILLUMENATE pivotal and pharmacokinetic studies. *Circulation* 2017; **136:** 1102–13.

6 Steiner S, Willfort-Ehringer A, Sievert H, et al. 12-month results from the first-in-human randomized study of the ranger paclitaxel-coated balloon for femoropopliteal treatment. *JACC Cardiovasc Interv* 2018; **11:** 934–41.

7 Rosenfield K, Jaff MR, White CJ, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease. *N Engl J Med* 2015; **373:** 145–53.

8 Thieme M, Von Bilderling P, Paetzel C, Karnabatidis D, Perez Delgado J, Lichtenberg M. The 24-month results of the Lutonix Global SFA Registry: worldwide experience with Lutonix drug-coated balloon. *JACC Cardiovasc Interv* 2017; **10:** 1682–90.

9 Dake MD, Ansel GM, Jaff MR, et al. Durable clinical effectiveness with paclitaxel-eluting stents in the femoropopliteal artery: 5-year results of the Zilver PTX Randomized Trial. *Circulation* 2016; **133:** 1472–83.

10 Iida O, Uematsu M, Soga Y, et al. Timing of the restenosis following nitinol stenting in the superficial femoral artery and the factors associated with early and late restenoses. *Catheter Cardiovasc Interv* 2011; **78:** 611–17.

11 Müller-Hülsbeck S, Keirse K, Zeller T, Schroe H, Diaz-Cartelle J. Long-term results from the MAJESTIC trial of the Eluvia paclitaxel-eluting stent for femoropopliteal treatment: 3-year follow-up. *Cardiovasc Interv Ther* 2017; **40:** 1832–38.

12 Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997; **26:** 517–38.

13 Stone GW, Teirstein PS, Meredith IT, et al. A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: the PLATINUM (a Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of Up to Two de Novo Coronary Artery Lesions) trial. *J Am Coll Cardiol* 2011; **57:** 1700–08.

14 Kelly CR, Teirstein PS, Meredith IT, et al. Long-term safety and efficacy of platinum chromium everolimus-eluting stents in coronary artery disease: 5-year results from the PLATINUM trial. *JACC Cardiovasc Interv* 2017; **10:** 2392–400.

15 Dake MD, Ansel GM, Jaff MR, et al. Paclitaxel-eluting stents show superiority to balloon angioplasty and bare metal stents in femoropopliteal disease: twelve-month Zilver PTX randomized study results. *Circ Cardiovasc Interv* 2011; **4:** 495–504.

16 Müller-Hülsbeck S, Keirse K, Zeller T, Schroe H, Diaz-Cartelle J. Twelve month results from the MAJESTIC trial of the Eluvia paclitaxel-eluting stent for treatment of obstructive femoropopliteal disease. *J Endovasc Ther* 2016; **23:** 701–07.

17 Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. *Catheter Cardiovasc Interv* 2007; **69:** 910–19.

18 Bisdas T, Beropoulis E, Argyriou A, Torsello G, Stavroulakis K. 1-year all-comers analysis of the Eluvia drug-eluting stent for long femoropopliteal lesions after suboptimal angioplasty. *JACC Cardiovasc Interv* 2018; **11:** 957–66.

19 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007; **45:** S5–67.

20 Rooke TW, Hirsch AT, Misra S, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **61:** 1555–70.

21 Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO), The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2017; **39:** 763–816.

22 Stage TB, Bergmann TK, Kroetz DL. Clinical pharmacokinetics of paclitaxel monotherapy: an updated literature review. *Clin Pharmacokinet* 2018; **57:** 7–19.

23 Dake MD, Scheinert D, Tepe G, et al. Nitinol stents with polymer-free paclitaxel coating for lesions in the superficial femoral and popliteal arteries above the knee: twelve-month safety and effectiveness results from the Zilver PTX single-arm clinical study. *J Endovasc Ther* 2011; **18:** 613–23.

24 Dake MD, Van Alstine WG, Zhou Q, Ragheb AO. Polymer-free paclitaxel-coated Zilver PTX stents—evaluation of pharmacokinetics and comparative safety in porcine arteries. *J Vasc Interv Radiol* 2011; **22:** 603–10.

25 Duda SH, Bosiers M, Lammer J, et al. Drug-eluting and bare nitinol stents for the treatment of atherosclerotic lesions in the superficial femoral artery: long-term results from the SIROCCO trial. *J Endovasc Ther* 2006; **13:** 701–10.

26 Lammer J, Bosiers M, Zeller T, et al. First clinical trial of nitinol self-expanding everolimus-eluting stent implantation for peripheral arterial occlusive disease. *J Vasc Surg* 2011; **54:** 394–401.

THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Gray WA, Keirse K, Soga Y, et al. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet* 2018; published online Sept 22. http://dx.doi.org/10.1016/S0140-6736(18)32262-1.

Supplementary Material

A polymer-coated paclitaxel-eluting stent (Eluvia) versus a polymer-free paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised trial

Table A1. Sites, investigators, core laboratories, study committees

Investigators and Centers				
Principal Investigator	**Sub-Investigators**	**Research Coordinators**	**Site Name**	**Location**
Thomas Albrecht	Goetz Eschenbach; Hanna Lehnkering	Gabriela Baumann; Antonia Ukrow	Vivantes Klinikum Neukoelln	Berlin, Germany
Kenji Ando	Takenori Domei; Seiichi Hiramori; Takashi Hiromasa; Takahiro Iseda; Akihiro Isotani; Nobuhrio Ito; Hisaki Masuda; Shintaro Mori; Yoshimitsu Soga; Yusuke Tomoi	N/A	Kokura Memorial Hospital	Fukuoka, Japan
Anvar Babaev	Michael Attubato; Stylianos Papadakos; Louai Razzouk; Claudia Serrano	Zulfiya Bakirova; Stanley Cobos; John Larigakis	New York University Medical Center	New York, NY, USA
Michael J. Bacharach	Tommy Reynolds	Patty Eisenbraun; Robin Farley	Avera Heart Hospital of South Dakota	Sioux Falls, SD, USA
William Bachinsky	David Chang; Cleon Hubbard; David Loran	Gretchen Meise; Laura Wells	Pinnacle Health Cardiovascular Institute	Wormleysburg, PA, USA
Danielle Bajakian	Philip Green; Ajay Kirtane; Anthony Pucillo; Nicholas Morrisey	Amanda Alonso; Ormarys Castellanos; Kate Dalton; Deniz Akkoc; Efrain DeJesus; Angeli Feri; Lorena Geilen; Andy Morales; Jeimy Rosado; Lorriane Vasi	Columbia University Medical Center	New York, NY, USA
Robert Beasley	Timothy Yates	Tamar Capehart; Jennifer Gimeno; Yoselin Lugo	Mount Sinai Medical Center	Miami Beach, FL, USA
James Benenati	Ripal Gandhi; Barry Katzen; Alex Powell; Brian James Schiro; Constantino Pena	Ivette Cruz; Sarah Alegre; Maria Ardid; Susan Arp; Sylvia Morales Olivares; Kathy Ortiz	Baptist Hospital of Miami	Miami, FL, USA
Andrew Benko	Francois Belzile	Guylaine Provencher	Fleurimont Hospital	Sherbrooke, QC, Canada
Mark Burket	Ehab Eltahawy; Rajesh Gupta; George Moukarbel; Ankush Moza; Mujeed Sheikh	Stephanie Frank; Kristin Fisher	University of Toledo Medical Center	Toledo, OH, USA

Investigators and Centers				
Principal Investigator	**Sub-Investigators**	**Research Coordinators**	**Site Name**	**Location**
Joseph Cardenas	Evren Husnu Kaynak	Yesenia Zambrano	Yuma Regional Medical Center	Yuma, AZ, USA
Tony Das	Tulio Diaz; Kenneth Saland; Victoria Skobel	Jennifer Beasley	Cardiovascular Research Institute of Dallas	Dallas, TX, USA
Randall De Martino	Haraldur Bjarnason	Alisa Diderrich; Jill Evjen; Lori Schmeling; Jean Wigham	Mayo Clinic Foundation	Rochester, MN, USA
Hannes Deutschmann	Marianne Brodmann; Peter Rief; Florian Schmid	Gabriele Platzer; Raphaela Rauter	Medizinische Univ.-Kliniken Graz	Graz, Austria
Daniel Dulas	Abdel Akef; Ashley Harrison; John Lee; William McMillian	Brittany Renier; Jill Stahlberg	Mercy Hospital	Coon Rapids, MN, USA
Robert Feldman	Richard Han; Gregory Von Mering	Rhonda Grubbs; Rebecca Sogan; Tabatha Wolter	Mediquest Research at Munroe Regional Medical Center	Ocala, FL, USA
Mark Fugate	Daniel Fisher; Michael Greer; Jeffrey Steven Horn; Charles Joels; Sachin Phade; L Sprouse	Laura Brown; Staci Higgins; Patricia Lewis	University Surgical Associates	Chattanooga, TN, USA
Lawrence Garcia	Alireza Vaziri	Margaret Michaelian	Steward St. Elizabeth's Medical Center of Boston, Inc.	Boston, MA, USA
Jaafer Golzar	Thomas Levin	Christopher Doherty; Diane Braun; Ann Gagliardi	Advocate Christ Medical Center	Oak Lawn, IN, USA
Rao Gutta	Jennifer Chavez	Melissa Romsa; Kristin Pendleton; Louis Rasmussen	CHI Bergan Mercy Hospital	Omaha, NE, USA
Patrick Hall	Hourman Tamaddon; Paul Riesenman	Jennifer Hansen; Lauren Baer	University Hospital	Augusta, GA, USA
Stewart Hawkins	Stuart Barnard; Daniel Cookson; Brendon O'Donoghue	Diane Caveney	Middlemore Hospital	Otahuhu, New Zealand
Steve Henao	Trent Proffitt; Richard Wilkerson	Jennifer Cordova; Maria Vahtel	New Mexico Heart Institute, PA	Albuquerque, NM, USA

Investigators and Centers				
Principal Investigator	**Sub-Investigators**	**Research Coordinators**	**Site Name**	**Location**
Benjamin Herdrich	Robert Brebrick; Dennis Costa; Ralph Fairchild	Jeff Kaliebe; Brian Acker	Aspirus Heart and Vascular Institute - Research and Education	Wausau, WI, USA
Keisuke Hirano	Motoharu Araki; Tomoya Fukagawa; Yohsuke Honda; Yoshiaki Ito; Norihiro Kobayashi; Toshihiko Kishida; Kenji Makino; Shinsuke Mori; Yasunari Sakamoto; Shigemitsu Shirai; Masakazu Tsutsumi; Masahiro Yamawaki	N/A	Saiseikai Yokohama-City Eastern Hospital	Kanagawa, Japan
Andrew Holden	Brendan Buckley; Brigid Connor; Andrew Hill; Stephan Merrilees	Helen Knight	Auckland City Hospital	Auckland, New Zealand
Safwan Jaalouk	F. Fleischhauer	Jennifer Lehmann; Tricia Parsons	Baptist Hospital	Pensacola, FL, USA
Sean Janzer	Jon George; Sanjog Kalra	Kinnari Murthy; Taylor Gandy	Albert Einstein Medical Center	Philadelphia, PA, USA
Daizo Kawasaki	Masashi Fukunaga; Tsuyoshi Nakata	N/A	Morinomiya Hospital	Osaka, Japan
Koen Keirse	Bart Joos; Sebastien Strypstein	Lies Vanermen; Stephanie Hermans	Regionaal Ziekenhuis Heilig Hart Tienen	Tienen, Belgium
Yazan Khatib	Sumith Aleti; Vagar Ali; Imraan Ansaarie; Omer Zuberi	Mary Hudson; Cheryl Cangemi; Erin Tucker	First Coast Cardiovascular	Jacksonville, FL, USA
Kimihiko Kichikawa	Shigeo Ichihashi; Shinichi Iwakoshi	N/A	Nara Medical University Hospital	Nara, Japan
Ethan Korngold	Bryant Ullery	Michelle Dixon; Ellen Muir	Providence St. Vincent Medical Center	Portland, OR, USA
Christian Loewe	Dietrich Beitzke; Martin Funovics; Domagoj Javor; Christian Kinstner; Christina Langenberger; Wolfgang Matzek; Richard Nolz; Stefan Puchner; Ruediger Schernthaner	Johanna Moyses; Ruth Swatosch; Maria Schoder; Fredrik Waneck; Florian Wolf	Allgemeines Krankenhaus AKH	Vienna, Austria
Louis Lopez	N/A	Cheryl Bair	St. Joseph Hospital	Fort Wayne, IN, USA

Investigators and Centers				
Principal Investigator	**Sub-Investigators**	**Research Coordinators**	**Site Name**	**Location**
Henry Lui	Heath Broussard; Gregory Bruno; John Crocker; Frederick Johnson	Mary Harris; Katherine Newman; Scott Sweat	Jackson-Madison County General Hospital	Jackson, TN, USA
Toshiaki Mano	Yosuke Hata; Osamu Iida; Takayuki Ishihara; Takashi Kanda; Hiroyuki Kawai; Kiyonori Nanto; Shin Okamoto; Shota Okuno; Aki Tsuji; Takuya Tsujimura	N/A	Kansai Rosai Hospital	Hyogo, Japan
Robert Mendes	George Adams; Dorian deFreitas; Matthew Hook; Jason Kim; Martyn Knowles; Mohit Pasi; Ravish Sachar; Joel Schneider; Willis Wu; James Zidar	Soumya Sidana; Lauren Koonce; Caroline Morton; Jamal Moss; Alexis McClellan	Rex Hospital	Raleigh, NC, USA
Akira Miyamoto	Takako Akita; Masahiro Fukuda; Naohiro Hakamata; Ryoji Kuhara; Takashi Maruyama; Masayuki Nakao; Chiaki Obara; Yasutaka Yamauchi	N/A	Takatsu General Hospital	Kanagawa, Japan
Stefan Müller-Hülsbeck	Silke Hopf-Jensen; Maximilian Heyko Leissner; Stepanie Lehrke; Michael Prieb; Leonardo Marques	Inga Petersen; Andrea Merkle; Markus Knoblauch	Ev. Luth. Diakonissenanstalt Flensburg	Flensburg, Germany
Masato Nakamura	Ryo Fukui; Hidehiko Hara; Raisuke Iijima; Nobutaka Ikeda; Tsuyoshi Ono; Hiroki Takenaka; Satoru Toi; Masahide Tokue; Mami Watanabe	N/A	Toho University Ohashi Medical Center	Tokyo, Japan
David O'Connor	Anjali Ratnathicam; Gregory Simonian; Massimo Napolitano; Michael Wilderman	Jana Tancredi; Patricia Arakelian; David Lai; Sora Limor	Hackensack University Medical Center	Hackensack, NJ, USA
Takao Ohki	Tadashi Abe; Takeshi Baba; Masayuki Hara; Koji Maeda; Masamichi Momose; Makiko Omori; Hiromasa Tachihara; Reo Takizawa; Masahiro Tezuka	N/A	The Jikei University Hospital	Tokyo, Japan

Investigators and Centers				
Principal Investigator	**Sub-Investigators**	**Research Coordinators**	**Site Name**	**Location**
James Park	Carter King; Parin Parikh	Elizabeth Justus; Lisa Carson	Presbyterian Hospital of Dallas	Dallas, TX, USA
Richard Powell	Jennifer Stabelford; David Stone; Bjoern Suckow	Wendy Aarino; Dorothy Hebb; Henry Stokes	Dartmouth Hitchcock Medical Center	Lebanon, NH, USA
Antonis Pratsos	Francis Day; Sarang Mangalmurti; Robert Meisner	Lynn Sher; Lisa Thome	Lankenau Institute for Medical Research	Bryn Mawr, PA, USA
Jeffery Prem	Brett Butler; Matthew Miller	Barabara Rambaud; Jeannie Archinal; Lacey Zerner	Aultman Hospital	Canton, OH, USA
Vikram Rao	David Rollins	Kathy Sheridan; Sam DiBlasio	LakeWest Hospital	Willoughby, OH, USA
John Rashid	Marco Barzallo; Gerri Hellhake-Hall; Sudhir Mungee; Elizabeth Schwandner	Stephanie Hillis	St. Francis Medical Center	Peoria, IL, USA
Robert Rhee	Alexander Shiferson; Michael Shih	Susan Beale; Louisa DiGerolamo	Maimonides Medical Center	Brooklyn, NY, USA
Jason Ricci	Louis Cannon; David Corteville; Duane Schuil; Anton Sharapov	Jennifer LaLonde; Jane Fisher; Tammy LaPeer; Joan Morey; Cindy Witucki	Northern Michigan Hospital	Petoskey, MI, USA
Dierk Scheinert	Yvonne Bausback; Manuela Matschuck; Corneliu-Gheorghe Popescu; Andrej Schmidt	Janine Brunotte; Ursula Banning-Eichenseer; Janin Lenzer	University Leipzig	Leipzig, Germany
Herman Schroë	Laura Kerselaers; Wouterus Lansink; Geert Lauwers	Wendy Zwinnen	Ziekenhuis Oost Limburg	Genk, Belgium
Henrik Schroeder	Alexandre Lucas; Marcello Martorana; Veronika Pizon; Ferdinand Ruecker; Christoph Wiemann	Manuela Schulz; Claudia Trautvetter	Center for Diagnostic Radiology and Minimally Invasive Therapy at The Jewish Hospital Berlin	Berlin, Germany
Peter O. Simon Jr.	Andrew Hines; Michael Meuse; David Sheridan; Daniel Stackhouse; Jason Swenson	Susan Steen	Carolinas HealthCare System NorthEast	Concord, NC, USA

Investigators and Centers				
Principal Investigator	**Sub-Investigators**	**Research Coordinators**	**Site Name**	**Location**
Gagan Singh	John Carson; David Dawson; Misty Humpheries; John Laird; William Pevec	Codi Cole; Kimberley Book	University of California, Davis Medical Center	Sacramento, CA, USA
Kongteng Tan	George Oreopoulos; Graham Roche-Nagle	Iris Zhong	Toronto General Hospital	Toronto, ON, Canada
Paul Tolerico	Nancy Harthun	Rebecca Eberly; Kim Botts	York Hospital	York, PA, USA
Thodur Vasudevan	Yen Yung Chieng; Zubayr Zaman	Anne Geoffic; Eileen Bisley	Clinical Trials NZ	Hamilton, New Zealand
Frank Vermassen	Annick D'Haeninck; Bart Doyen; Francis Goudsmedt; Nathalie Moreels; Caren Randon; Isabelle Van Herzeele	Mia Geenens	Universitair Ziekenhuis Gent	Gent, Belgium
Martin Werner	Heribert Scheck; Reinhold Tischler	Mathias Tischler	Hanusch-Krankenhaus	Wien, Austria
Bret Wiechmann	Bryson Wesley Mann	Kurt Malphurs; Charles David; Heather Rausch	Florida Research Network, LLC	Gainesville, FL, USA
Hiroyoshi Yokoi	Yutaka Fukuizumi; Takahiro Inoue; Yuji Murakami; Koji Ozaki; Michitaka Sugeno; Toshie Tanaka	N/A	Fukuoka Sanno Hospital	Fukuoka, Japan
Yoshiaki Yokoi	Masahiko Fujihara; Keisuke Fukuda; Akihiro Higashimori; Nobuyuki Morioka; Shinji Shiotani	N/A	Kishiwada Tokushukai Hospital	Osaka, Japan
Thomas Zeller	Ulrich Beschorner; Tanja Böhme; Karl-Heinz Bürgelin; Börries Jacques; Cornelia Lindemann; Elias Noory; Stephanie Schlosser; Krista Schoellhorn	Claudia Maas; Ria Bschor; Sonja Haberstroh; Monika Rubin-Fedrich; Sabine Schonhardt; Jochen Struebin; Margarethe Welslau; Verena Zaehringer	Herzzentrum Bad Krozingen	Bad Krozingen, Germany

CEC Members	
Name	**Institute**
CEC Chairman: David Hurrell, M.D.	Minneapolis Cardiology Associates
Jeffrey Chambers, M.D.	Metropolitan Cardiology Consultants
David Laxson, M.D.	University of Minnesota Physicians
Yale Wang, M.D.	Minneapolis Heart Institute
Robert Wilson, M.D.	University of Minnesota Cardiovascular Division
Independent Data Reviewer	
Name	**Institute**
Alan H. Matsumoto, M.D.	University of Virginia Health System

Core Laboratories		
Angiographic Core Laboratory:	Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center (BIDMC)	Jeffrey J. Popma, MD; Alexandra Almonacid Popma, MD
Vascular Ultrasound and X-ray Core Laboratory:	Massachusetts General Physicians Organization – Vascular Ultrasound Core Laboratory (MGPO, Vascore)	Gail Hadley; Dr. Ido Weinberg
Pharmacokinetics Core Laboratory:	Covance Central Laboratory Services LP	

Boston Scientific Research Support	
Name	**Title**
Anastasia Becker	Clinical Trials Director
Lieve Cornelis	Senior Clinical Project Manager
Jennifer Hansen	Senior Clinical Program Manager
Deb Jovanovich	Senior Clinical Trial Manager (former employee)
Nicole Kilburn	Clinical Trial Manager
Rieko Kuribayashi	Senior Project Manager
Naoko Takahashi	Clinical Program Manager
Megan White	Senior Clinical Trials Specialist

Table A2. Inclusion and exclusion criteria

Inclusion Criteria

1. Subjects age 18 and older.
2. Subject (or Legal Guardian if applicable) is willing and able to provide consent before any study-specific test or procedure is performed, signs the consent form, and agrees to attend all required follow-up visits. NOTE: For subjects less than 20 years of age enrolled at a Japanese centre, the subject's legal representative, as well as the subject, must provide written informed consent.
3. Chronic, symptomatic lower limb ischemia defined as Rutherford categories 2, 3 or 4.
4. Stenotic, restenotic or occlusive lesion(s) located in the native SFA and/or PPA:
    a. Degree of stenosis ≥70% by visual angiographic assessment
    b. Vessel diameter ≥ 4 and ≤ 6 mm
    c. Total lesion length (or series of lesions) ≥ 30 mm and ≤ 140 mm (Note: Lesion segment(s) must be fully covered with one ELUVIA stent or up to two Zilver PTX stents)
    d. For occlusive lesions requiring use of re-entry device, lesion length ≤ 120 mm
    e. Target lesion located at least three centimetres above the inferior edge of the femur
5. Patent infrapopliteal and popliteal artery, i.e., single vessel runoff or better with at least one of three vessels patent (<50% stenosis) to the ankle or foot with no planned intervention.

Exclusion Criteria

1. Previously stented target lesion/vessel.
2. Target lesion/vessel previously treated with drug-coated balloon < 12 months prior to randomisation/enrolment.
3. Subjects who have undergone prior surgery of the SFA/PPA in the target limb to treat atherosclerotic disease.
4. Use of atherectomy, laser or other debulking devices in the target limb SFA/PPA during the index procedure.
5. History of major amputation in the target limb.
6. Documented life expectancy less than 24 months due to other medical co-morbid condition(s) that could limit the subject's ability to participate in the clinical study, limit the subject's compliance with the follow-up requirements, or impact the scientific integrity of the clinical study.
7. Known hypersensitivity or contraindication to contrast dye that, in the opinion of the investigator, cannot be adequately pre-medicated.
8. Known hypersensitivity/allergy to the investigational stent system or protocol related therapies (e.g., nitinol, paclitaxel, or structurally related compounds, polymer or individual components, and antiplatelet, anticoagulant, thrombolytic medications).
9. Platelet count < 80,000 mm^3 or > 600,000 mm^3 or history of bleeding diathesis.
10. Concomitant renal failure with a serum creatinine > 2.0 mg/dL.
11. Receiving dialysis or immunosuppressant therapy.
12. History of myocardial infarction (MI) or stroke/cerebrovascular accident (CVA) within 6 months prior to randomisation/enrolment.
13. Unstable angina pectoris at the time of randomisation/enrolment.
14. Pregnant, breast feeding, or plan to become pregnant in the next 5 years.
15. Current participation in another investigational drug or device clinical study that has not completed the primary endpoint at the time of randomisation/enrolment or that clinically interferes with the current study endpoints (Note: studies requiring extended follow-up for products that were investigational, but have become commercially available since then are not considered investigational studies).
16. Septicaemia at the time of randomisation/enrolment.
17. Presence of other hemodynamically significant outflow lesions in the target limb requiring intervention within 30 days of randomisation/enrolment.
18. Presence of aneurysm in the target vessel.
19. Acute ischemia and/or acute thrombosis of the SFA/PPA prior to randomisation/enrolment.
20. Perforated vessel as evidenced by extravasation of contrast media prior to randomisation/enrolment.
6. Heavily calcified lesions.

Table A3. Stent lengths and diameters available for use in IMPERIAL

	Length					
Diameter	**40 mm**	**60 mm**	**80 mm**	**100 mm**	**120 mm**	**150 mm**
6.0 mm	E, Z	E, Z	E, Z	E, Z	E, Z	E
7.0 mm	E, Z	E, Z	E, Z	E, Z	E, Z	E

Eluvia stent (E) working lengths: 75 cm, 130 cm; Zilver PTX stent (Z) working lengths: 80 cm, 125 cm. Use of two overlapping Zilver PTX stents was allowed according to the device Instructions for Use.

Table A4. Safety and effectiveness at 12 months: primary endpoint testing of non-inferiority[*]

	Eluvia (N=274)	Zilver PTX (N=135)	Difference [95% CI]	One-sided 95% Farrington-Manning Lower Confidence Bound	Non-Inferiority p-value
Intention-to-treat					
Primary Patency[†]	86.8% (231/266)	81.5% (106/130)	5.3% [-2.5%, 13.1%]	- 0.66%	<0.0001
MAE[‡]-Free	94.9% (259/273)	91.0% (121/133)	3.9% [-1.6%, 9.4%]	- 0.46%	<0.0001
Per protocol					
Primary Patency[†]	87.1% (229/263)	81.0% (102/126)	6.1% [-1.8%, 14.1%]	0.08%	<0.0001
MAE[‡]-Free	95.2% (257/270)	90.7% (117/129)	4.5% [-1.1%, 10.1%]	0.09%	<0.0001

[*]Analysis of the primary noninferiority endpoints for safety and effectiveness occurred when the minimum number of patients required for adequate statistical power had completed 12-month follow-up (ie, approximately 85% of the full cohort of study patients). The per-protocol cohort was determined from this initial intention-to-treat patient set.

[†]Duplex ultrasound peak systolic velocity ratio ≤ 2·4 at the 12-month follow-up visit, in the absence of clinically-driven target lesion revascularisation or bypass of the target lesion. [‡]All causes of death through 1 month, target limb major amputation through 12 months and/or target lesion revascularisation through 12 months.

Table A5. Health-related quality of life (EQ5D) dimensions

		ELUVIA			
EQ-5D Dimension	**Level**	**Baseline**	**1-Month**	**6-Month**	**12-Month**
Mobility	No problems	16.3% (50/306)	55.7% (170/305)	55.1% (161/292)	54.8% (154/281)
	Slight problems	18.3% (56/306)	23.0% (70/305)	25.0% (73/292)	19.2% (54/281)
	Moderate problems	36.3% (111/306)	16.4% (50/305)	11.6% (34/292)	16.7% (47/281)
	Severe problems	28.4% (87/306)	4.6% (14/305)	7.2% (21/292)	7.8% (22/281)
	Unable	0.7% (2/306)	0.3% (1/305)	1.0% (3/292)	1.4% (4/281)
Personal Care	No problems	89.2% (273/306)	92.8% (283/305)	93.5% (273/292)	92.2% (259/281)
	Slight problems	5.9% (18/306)	4.6% (14/305)	2.4% (7/292)	4.3% (12/281)
	Moderate problems	3.9% (12/306)	2.0% (6/305)	2.7% (8/292)	2.5% (7/281)
	Severe problems	1.0% (3/306)	0.7% (2/305)	1.0% (3/292)	0.4% (1/281)
	Unable	0.0% (0/306)	0.0% (0/305)	0.3% (1/292)	0.7% (2/281)
Usual Activities	No problems	44.4% (136/306)	72.8% (222/305)	71.9% (210/292)	71.9% (202/281)
	Slight problems	21.9% (67/306)	15.4% (47/305)	14.7% (43/292)	14.2% (40/281)
	Moderate problems	20.6% (63/306)	8.9% (27/305)	8.9% (26/292)	9.6% (27/281)
	Severe problems	10.1% (31/306)	2.6% (8/305)	3.4% (10/292)	2.8% (8/281)
	Unable	2.9% (9/306)	0.3% (1/305)	1.0% (3/292)	1.4% (4/281)
Pain/Discomfort	None	23.9% (73/306)	47.2% (144/305)	47.9% (140/292)	49.5% (139/281)
	Slight	22.2% (68/306)	33.1% (101/305)	27.7% (81/292)	22.4% (63/281)
	Moderate	30.1% (92/306)	14.1% (43/305)	16.1% (47/292)	18.5% (52/281)
	Severe	21.9% (67/306)	5.2% (16/305)	7.2% (21/292)	8.5% (24/281)
	Extreme	2.0% (6/306)	0.3% (1/305)	1.0% (3/292)	1.1% (3/281)
Anxiety/Depression	None	69.9% (214/306)	78.7% (240/305)	77.1% (225/292)	77.6% (218/281)
	Slight	15.7% (48/306)	14.8% (45/305)	11.0% (32/292)	14.9% (42/281)
	Moderate	12.4% (38/306)	5.2% (16/305)	9.2% (27/292)	5.0% (14/281)
	Severe	1.6% (5/306)	1.0% (3/305)	2.4% (7/292)	1.8% (5/281)
	Extreme	0.3% (1/306)	0.3% (1/305)	0.3% (1/292)	0.7% (2/281)
EQ-5D Index Values (model from the US)		0.7±0.2 (306) (0.0, 1.0)	0.9±0.1 (305) (0.2, 1.0)	0.8±0.2 (292) (0.0, 1.0)	0.8±0.2 (281) (-0.1, 1.0)
EQ Visual Analogue Scale		66.4±17.6 (306) (0.0, 100.0)	74.0±17.3 (305) (0.0, 100.0)	74.0±15.6 (292) (25.0, 100.0)	73.0±17.8 (281) (10.0, 100.0)
		Zilver PTX			
EQ-5D Dimension	**Level**	**Baseline**	**1-Month**	**6-Month**	**12-Month**
Mobility	No problems	19.2% (30/156)	53.6% (82/153)	51.7% (74/143)	51.4% (73/142)
	Slight problems	19.9% (31/156)	27.5% (42/153)	24.5% (35/143)	21.1% (30/142)
	Moderate problems	36.5% (57/156)	16.3% (25/153)	16.8% (24/143)	17.6% (25/142)

	Severe problems	24.4% (38/156)	2.0% (3/153)	7.0% (10/143)	7.0% (10/142)
	Unable	0.0% (0/156)	0.7% (1/153)	0.0% (0/143)	2.8% (4/142)
Personal Care	No problems	89.1% (139/156)	88.9% (136/153)	88.8% (127/143)	90.1% (128/142)
	Slight problems	6.4% (10/156)	9.2% (14/153)	9.1% (13/143)	4.9% (7/142)
	Moderate problems	4.5% (7/156)	1.3% (2/153)	0.7% (1/143)	2.8% (4/142)
	Severe problems	0.0% (0/156)	0.7% (1/153)	1.4% (2/143)	2.1% (3/142)
	Unable	0.0% (0/156)	0.0% (0/153)	0.0% (0/143)	0.0% (0/142)
Usual Activities	No problems	47.4% (74/156)	66.7% (102/153)	69.9% (100/143)	65.5% (93/142)
	Slight problems	23.7% (37/156)	17.0% (26/153)	16.1% (23/143)	16.9% (24/142)
	Moderate problems	19.9% (31/156)	11.8% (18/153)	7.7% (11/143)	12.0% (17/142)
	Severe problems	6.4% (10/156)	3.9% (6/153)	6.3% (9/143)	2.8% (4/142)
	Unable	2.6% (4/156)	0.7% (1/153)	0.0% (0/143)	2.8% (4/142)
Pain/Discomfort	None	26.3% (41/156)	54.2% (83/153)	52.4% (75/143)	43.0% (61/142)
	Slight	25.6% (40/156)	24.2% (37/153)	18.9% (27/143)	33.8% (48/142)
	Moderate	24.4% (38/156)	16.3% (25/153)	20.3% (29/143)	13.4% (19/142)
	Severe	21.8% (34/156)	3.3% (5/153)	7.7% (11/143)	8.5% (12/142)
	Extreme	1.9% (3/156)	2.0% (3/153)	0.7% (1/143)	1.4% (2/142)
Anxiety/Depression	None	69.9% (109/156)	77.8% (119/153)	81.1% (116/143)	75.4% (107/142)
	Slight	17.3% (27/156)	13.7% (21/153)	11.9% (17/143)	11.3% (16/142)
	Moderate	9.0% (14/156)	4.6% (7/153)	5.6% (8/143)	10.6% (15/142)
	Severe	3.2% (5/156)	3.9% (6/153)	0.7% (1/143)	1.4% (2/142)
	Extreme	0.6% (1/156)	0.0% (0/153)	0.7% (1/143)	1.4% (2/142)
EQ-5D Index Values (model from the US)		0.8±0.1 (156) (0.3, 1.0)	0.8±0.1 (153) (0.2, 1.0)	0.9±0.1 (143) (0.3, 1.0)	0.8±0.2 (142) (-0.1, 1.0)
EQ Visual Analogue Scale		68.7±17.8 (156) (0.0, 100.0)	75.6±17.4 (153) (0.0, 100.0)	76.6±16.7 (143) (30.0, 100.0)	75.8±18.2 (142) (10.0, 100.0)

Table A6. Hospitalization rates

	Eluvia (N=309)	Zilver PTX (N=156)	Overall (N=465)
Readmission Rate			
1 Month	1.0% (3/309)	2.6% (4/156)	1.5% (7/465)
6 Months	2.3% (7/309)	3.8% (6/156)	2.8% (13/465)
12 Months	3.9% (12/309)	7.1% (11/156)	4.9% (23/465)
Number of days in hospital since index procedure			
For all AE	13.9±27.3 (123)	17.7±30.2 (60)	15.1±28.2 (183)
For TLR/TVR	2.8±2.7 (22)	7.1±11.9 (17)	4.7±8.2 (39)
For Procedure/Device Related AE	2.7±2.7 (17)	4.5±5.9 (15)	3.5±4.5 (32)

Note: Readmission Rate represents (# of subjects/Total enrolled subjects) who were hospitalized due to TLR/TVR or due to site-assessed Procedure/Device related AE. "Number of days in hospital" is cumulative and contains all days irrespective of number of hospitalizations.

Table A7. Site-reported adverse event rates to 12 months

	Eluvia (N=309)	Zilver PTX (N=156)	Difference [95% CI]	p-value
Adverse Event Rate	68.3% (211/309)	68.6% (107/156)	-0.3% [-9.2%, 8.6%]	0.9468
Unanticipated	0.0% (0/309)	0.0% (0/156)	0.0% [NA, NA]	Undef
Serious	41.4% (128/309)	42.3% (66/156)	-0.9% [-10.4%, 8.6%]	0.8552
Device-Related	8.1% (25/309)	14.1% (22/156)	-6.0% [-12.3%, 0.2%]	0.0423
Procedure-Related	19.1% (59/309)	17.3% (27/156)	1.8% [-5.6%, 9.2%]	0.6395

Table A8. Frequency of site-reported serious adverse events to 12 months

Serious Adverse Event		Eluvia (N=309)		Zilver PTX (N=156)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**Events**	**Rate of Subjects with Event**	**Events**	**Rate of Subjects with Event**	**p-value**
Total	Total	242	41.4% (128/309)	140	42.3% (66/156)	0.8552
Vascular disorders	Total	93	22.3% (69/309)	55	25.0% (39/156)	0.5197
	Peripheral artery stenosis	36	10.0% (31/309)	24	12.8% (20/156)	0.3636
	Intermittent claudication	20	5.8% (18/309)	11	6.4% (10/156)	0.8023
	Peripheral arterial occlusive disease	9	2.9% (9/309)	6	3.8% (6/156)	0.5906
	Femoral artery occlusion	8	2.6% (8/309)	5	2.6% (4/156)	1.0000
	Peripheral artery thrombosis	8	2.3% (7/309)	3	1.9% (3/156)	1.0000
	Extremity necrosis	3	0.6% (2/309)	0	0.0% (0/156)	0.5532
	Peripheral vascular disorder	2	0.6% (2/309)	2	1.3% (2/156)	0.6050
	Haematoma	2	0.6% (2/309)	0	0.0% (0/156)	0.5532
	Peripheral embolism	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Arterial spasm	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Arteriosclerosis	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Embolism	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Subclavian artery stenosis	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Peripheral ischaemia	0	0.0% (0/309)	2	1.3% (2/156)	0.1121
	Aortic aneurysm	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Cardiac disorders	Total	32	7.4% (23/309)	20	9.6% (15/156)	0.4195
	Angina pectoris	8	2.3% (7/309)	1	0.6% (1/156)	0.2775
	Coronary artery disease	4	1.3% (4/309)	1	0.6% (1/156)	0.6679
	Atrial fibrillation	3	1.0% (3/309)	3	1.9% (3/156)	0.4079
	Cardiac failure	3	1.0% (3/309)	2	1.3% (2/156)	1.0000
	Acute myocardial infarction	3	1.0% (3/309)	1	0.6% (1/156)	1.0000
	Coronary artery stenosis	2	0.3% (1/309)	4	1.9% (3/156)	0.1121
	Angina unstable	2	0.6% (2/309)	1	0.6% (1/156)	1.0000
	Cardiac failure congestive	2	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Cardiac arrest	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Atrial flutter	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Ischaemic cardiomyopathy	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Myocardial infarction	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Myocardial ischaemia	1	0.3% (1/309)	0	0.0% (0/156)	1.0000

Serious Adverse Event		Eluvia (N=309)		Zilver PTX (N=156)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**Events**	**Rate of Subjects with Event**	**Events**	**Rate of Subjects with Event**	**p-value**
	Cardiac failure chronic	0	0.0% (0/309)	2	1.3% (2/156)	0.1121
	Cardiopulmonary failure	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Mitral valve incompetence	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Tricuspid valve stenosis	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Infections and infestations	Total	18	3.9% (12/309)	21	8.3% (13/156)	0.0446
	Pneumonia	6	1.6% (5/309)	5	3.2% (5/156)	0.3144
	Pneumonia bacterial	2	0.6% (2/309)	0	0.0% (0/156)	0.5532
	Gangrene	1	0.3% (1/309)	4	1.3% (2/156)	0.2617
	Cellulitis	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Gastroenteritis	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Sepsis	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Urosepsis	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Clostridium difficile infection	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Erysipelas	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Infected skin ulcer	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Pneumonia pneumococcal	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Post procedural cellulitis	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Appendicitis	0	0.0% (0/309)	2	0.6% (1/156)	0.3355
	Bronchitis	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Catheter site infection	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Lung abscess	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Osteomyelitis	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Pneumonia viral	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Urinary tract infection	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Musculoskeletal and connective tissue disorders	Total	14	4.2% (13/309)	7	3.8% (6/156)	0.8527
	Pain in extremity	2	0.6% (2/309)	3	1.3% (2/156)	0.6050
	Intervertebral disc protrusion	2	0.6% (2/309)	1	0.6% (1/156)	1.0000
	Foot deformity	2	0.6% (2/309)	0	0.0% (0/156)	0.5532
	Spinal pain	2	0.6% (2/309)	0	0.0% (0/156)	0.5532
	Arthralgia	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Osteoarthritis	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Costochondritis	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Groin pain	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Musculoskeletal pain	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Osteochondritis	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Spinal osteoarthritis	0	0.0% (0/309)	1	0.6% (1/156)	0.3355

Serious Adverse Event		Eluvia (N=309)		Zilver PTX (N=156)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**Events**	**Rate of Subjects with Event**	**Events**	**Rate of Subjects with Event**	**p-value**
Gastrointestinal disorders	Total	14	3.9% (12/309)	3	1.9% (3/156)	0.2586
	Oesophagitis	2	0.6% (2/309)	0	0.0% (0/156)	0.5532
	Abdominal pain	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Inguinal hernia	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Abdominal pain upper	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Coeliac artery stenosis	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Diverticulum intestinal	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Dysphagia	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Epiploic appendagitis	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Intestinal haemorrhage	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Intestinal obstruction	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Pancreatitis	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Peptic ulcer	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Small intestinal obstruction	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Gastrointestinal haemorrhage	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Nervous system disorders	Total	12	3.6% (11/309)	7	3.8% (6/156)	0.8766
	Carotid artery stenosis	2	0.6% (2/309)	3	1.9% (3/156)	0.3402
	Transient ischaemic attack	2	0.6% (2/309)	0	0.0% (0/156)	0.5532
	Carotid artery occlusion	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Cerebrovascular accident	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Generalised tonic-clonic seizure	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Hemiparesis	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Ischaemic stroke	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Presyncope	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Sciatica	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Syncope	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Cerebral haemorrhage	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Cervicobrachial syndrome	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Encephalopathy	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Hepatic encephalopathy	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Total	10	2.6% (8/309)	4	2.6% (4/156)	1.0000

Serious Adverse Event		Eluvia (N=309)		Zilver PTX (N=156)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**Events**	**Rate of Subjects with Event**	**Events**	**Rate of Subjects with Event**	**p-value**
Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	6	1.3% (4/309)	1	0.6% (1/156)	0.6679
	Dyspnoea	2	0.6% (2/309)	0	0.0% (0/156)	0.5532
	Interstitial lung disease	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Respiratory failure	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Acute respiratory failure	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Pulmonary embolism	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Pulmonary oedema	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Injury, poisoning and procedural complications	Total	9	2.6% (8/309)	7	4.5% (7/156)	0.2740
	Vascular procedure complication	3	1.0% (3/309)	1	0.6% (1/156)	1.0000
	Fall	2	0.6% (2/309)	0	0.0% (0/156)	0.5532
	Post procedural haemorrhage	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Femur fracture	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Hip fracture	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Lumbar vertebral fracture	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Alcohol poisoning	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Laceration	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Procedural complication	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Spinal compression fracture	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Wound	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
General disorders and administration site conditions	Total	9	1.9% (6/309)	4	2.6% (4/156)	0.7382
	Non-cardiac chest pain	3	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Catheter site haematoma	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Death	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Chest pain	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	General physical health deterioration	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Impaired healing	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Multi-organ failure	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Therapeutic response decreased	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Treatment failure	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Blood and lymphatic system disorders	Total	9	2.3% (7/309)	0	0.0% (0/156)	0.1012
	Anaemia	6	1.6% (5/309)	0	0.0% (0/156)	0.1736
	Haemorrhagic anaemia	2	0.6% (2/309)	0	0.0% (0/156)	0.5532
	Thrombocytopenia	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
Neoplasms benign, malignant and	Total	7	1.9% (6/309)	3	1.9% (3/156)	1.0000
	Colon cancer	2	0.6% (2/309)	0	0.0% (0/156)	0.5532

Serious Adverse Event		Eluvia (N=309)		Zilver PTX (N=156)		
MedDRA System Organ Class	**MedDRA Preferred Term**	**Events**	**Rate of Subjects with Event**	**Events**	**Rate of Subjects with Event**	**p-value**
unspecified (incl cysts and polyps)	Oral neoplasm benign	2	0.3% (1/309)	0	0.0% (0/156)	1.0000
	B-cell lymphoma	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Hepatocellular carcinoma	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Prostate cancer metastatic	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Lymphoma	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Ovarian cancer	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
	Prostate cancer	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Skin and subcutaneous tissue disorders	Total	3	1.0% (3/309)	2	1.3% (2/156)	1.0000
	Diabetic foot	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Dry gangrene	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Intertrigo	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Skin ulcer	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Renal and urinary disorders	Total	3	1.0% (3/309)	1	0.6% (1/156)	1.0000
	Renal artery stenosis	2	0.6% (2/309)	0	0.0% (0/156)	0.5532
	Renal failure	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Renal failure acute	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Endocrine disorders	Total	3	1.0% (3/309)	0	0.0% (0/156)	0.5541
	Endocrine disorder	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Goitre	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Hyperthyroidism	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
Metabolism and nutrition disorders	Total	2	0.6% (2/309)	2	1.3% (2/156)	0.6050
	Dehydration	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Hypoglycaemia	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Fluid overload	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Psychiatric disorders	Total	1	0.3% (1/309)	2	0.6% (1/156)	1.0000
	Depression	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Alcohol abuse	0	0.0% (0/309)	2	0.6% (1/156)	0.3355
Ear and labyrinth disorders	Total	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Sudden hearing loss	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Tinnitus	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Eye disorders	Total	1	0.3% (1/309)	1	0.6% (1/156)	1.0000
	Retinal detachment	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Macular degeneration	0	0.0% (0/309)	1	0.6% (1/156)	0.3355
Reproductive system and breast disorders	Total	1	0.3% (1/309)	0	0.0% (0/156)	1.0000
	Breast disorder	1	0.3% (1/309)	0	0.0% (0/156)	1.0000

"Events" numbers are total episodes of each type of event among all subjects.
"Rate of Subjects with Event" numbers are percent of subjects who experienced one or more episodes of the event.
"Events" numbers for "TOTAL" are the sum of the individual event category totals.
"Rate of Subjects with Event" numbers for "TOTAL" is the percent of subjects who experienced an adverse event.