Original article

Systemic exposure of sirolimus after coronary stent implantation in patients with de novo coronary lesions: Supralimus-Core[®] pharmacokinetic study

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KEY WORDS

Drug-eluting stent
Percutaneous coronary intervention
Pharmacokinetics
Sirolimus

A B S T R A C T

Objectives: This study was conducted to assess the systemic drug release and distribution of sirolimus-eluting coronary stents.

Methods: Twenty patients with coronary artery disease (CAD) were treated with 1, 2, or 3 a newly designed metallic stents. Blood samples were drawn at 14 time points to determine the pharmacokinetic of sirolimus. Whole blood concentrations of sirolimus were determined by using a sensitive validated high-performance liquid chromatography mass spectrometry/mass spectrometry method.

Results: Minimal measurable blood levels were detectable at 7 days. Across all dose levels, individual T_{max} values ranged from 1.00 hour and 12.00 hours; individual C_{max} ranged from 0.73 ng/mL and 4.13 ng/mL.

Conclusion: This study confirms the limited exposure of the systemic circulation of the eluted drug with the use of the Supralimus-Core[®] Sirolimus-Eluting Coronary Stent System (Sahajanand Medical Technologies Pvt. Ltd., Surat, India). In this study, sirolimus concentration in systemic circulation is to be safe, well-tolerated and short-lived.

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Introduction

Fixed drug release kinetics and vessel wall partitioning may limit the effectiveness of present drug-eluting stents (DES).^{1–3} A new type of metallic stent has been engineered specifically as a next-generation coronary drug delivery system that allows precise and programmable control over special and temporal release kinetics. Drug-eluting stents are widely used for the treatment of coronary artery disease (CAD) due to significant improvement in angiographic outcome, with reduced rates of restenosis and need for revascularisation compared with bare metal stents (BMS).^{4–6} The Supralimus-Core[®] Sirolimus-Eluting Coronary Artery Stent System has proven its safety and efficacy in the first-in-man study. The Supralimus-Core[®]

is sirolimus-eluting stent (SES) with CE-approved Coronium[®] (L605 Co-Cr) bare metallic stent platform. sirolimus was first isolated from a soil micro-organism, *Streptomyces hygroscopicus*, found on Easter Island, as reported in 1975.⁷

Sirolimus binds avidly to an intracellular protein, called FK-binding protein (FKBP), which is up-regulated after vascular injury. Sirolimus-FKBP then binds to a critical signal transduction protein, called mammalian target of Rapamycin (m-TOR). The sirolimus-FKBP-m-TOR complex interferes with cell-cycle events such as blocking proteins that activate the cell-cycle, stimulating natural cell-cycle inhibitors and turning off the cell-cycle at the G₁-S phase.⁸ In vivo studies in allograft and angioplasty models demonstrated the effectiveness of sirolimus in preventing tissue hyperplasia following vascular injury and led to its consideration as an agent for the prevention of restenosis.^{9–10} Thus, release of sirolimus from stent, locally prevents neointimal hyperplasia. However, the concentration

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of sirolimus in the systemic circulation due to its local release from stent must be below the concentration which results in immune system suppression. Pharmacokinetics of sirolimus after implantation of SES has been studied in some of the animal studies using porcine model.^{11,12} With the aim of studying the pharmacokinetics of sirolimus after implantation of SES in human, Supralimus-Core[®] pharmacokinetic study was conducted.

Methods

This pharmacokinetics study was a multicentric, non-randomised, open label, uncontrolled, single group assignment conducted at four sites in which all patients received 1, 2, or 3 Supralimus-Core[®] SES. Out of a total of 20 patients enrolled in the study, 17 patients had single stent placement while two patients had two stents and one patient had three stents implanted. A total of 24 numbers of Supralimus-Core[®] stents were implanted in 20 patients. Supralimus-Core[®] SES loaded with a sirolimus dose of 1.4 µg/mm² was used in this study.

During percutaneous coronary intervention procedure, heparin boluses were intravenously administered and were additionally given if needed. Target lesions were treated with standard interventional techniques, including balloon predilation before SES implantation.

The study was conducted in full compliance with ICH-GCP (July, 2002), the Declaration of Helsinki and all other regulatory requirements. The study protocol was approved by the local hospital ethics committees of all participating centres and Central Drugs Standard Control Organization.

Inclusion criteria

Patients included in the study were more than 18-years of age with symptomatic ischaemic heart disease (IHD) with de novo stenotic coronary lesion with reference vessel diameter (RVD) of ≥ 2.5 mm and ≤ 3.5 mm. Patient or patient's legal representative were informed of the nature of the study and agreed to its provisions and had provided written informed consent as notified/approved by the Institutional Review Board/Ethics Committee of the clinical site.

Exclusion criteria

Patients were excluded if any of the following conditions were present: *General exclusion criteria:* 1) Women of childbearing potential; 2) acute or chronic renal dysfunction (creatinine > 2.0 mg/dL or > 150 µmol/L); 3) any patient who has a platelet count $< 100,000$ cells/mm³ or $> 700,000$ cells/mm³, a white blood cell of < 3000 cells/mm³; 4) evidence of an acute Q-wave or non-Q-wave myocardial infarction within 72-hours preceding the index procedure; 5) restenotic or lesion in graft; 6) patient with a life expectancy less < 12 months; 7) known allergies to aspirin, clopidogrel bisulphate (Plavix[®]), ticlopidine (Ticlid[®]), heparin or cobalt chromium; 8) any significant

Figure 1 Cumulative in vitro release profile of sirolimus from Supralimus-Core[®] sirolimus-eluting stent.

medical condition which in the investigator's opinion may interfere with the patient's optimal participation in the study; 9) currently participating in an investigational drug, or another device study, or subject to inclusion in another investigational drug, or another device study during follow-up; 10) previous bare metal stenting (< 1 year) anywhere within the target vessel or previous DES anywhere within any epicardial vessel; and 11) any contraindication to blood sampling.

Angiographic exclusion criteria: 1) Unprotected left main CAD with $\geq 50\%$ stenosis; 2) angiographic evidence of thrombus; 3) ejection fraction (EF) $\leq 25\%$; and 4) heavily calcified lesion and/or calcified lesion which cannot be successfully predilated.

Description of the study stent

Supralimus-Core[®] (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) has L605 Co-Cr alloy as its stent platform having strut thickness of 60 µm with biodegradable polymers and drug load of 1.4 µg/mm². About 70% of drug is released within 7 days and remaining drug is released over a period of 48 days (Figure 1). The coating layer comprises of drug sirolimus blended together with biodegradable polymeric matrix. This matrix includes different biodegradable polymers—Poly-L-Lactide, 50/50 Poly-DL-Lactide-co-Glycolide and Polyvinyl Pyrrolidone to control the drug elution from stent coating. After releasing the drug within 48-days, these polymers eventually degrades naturally and are excreted from the body in the form of their metabolites. The average coating thickness of Supralimus-Core[®] stent is between 5–6 µm.

Interventional procedure and adjunctive medications

All patients were on aspirin in a dose of 75–150 mg at least 24-hours prior to the procedure. A loading dose of 300 mg of clopidogrel was given 24-hours prior to procedure or 600 mg on the day of the procedure was given to patients before procedure. During the procedure, initial dose of 70–100 IU/kg bolus of heparin was given to the patient. Additional heparin was used, if necessary, during procedure to achieve activated

coagulation time >250 seconds. Administration of glycoprotein (GP) IIb/IIIa inhibitor was left to the investigator's discretion. Angiographic success was defined as $\leq 20\%$ stenosis by visual estimation.

Blood sampling

From each patient, 14 venous blood samples (each of 5 mL) were drawn at different time intervals. The blood samples were taken at baseline (before stent placement), at 10 and 30 minutes, at 1, 2, 4, 6, 12, 24, 72, 168, 336, 672, and 1152 hours after placement of the last DES. Blood samples were anticoagulated with potassium ethylenediaminetetraacetic acid (EDTA) and stored at -20°C until analysis.

Laboratory analysis method

Sirolimus in whole blood was assayed by a liquid chromatography-tandem mass spectrometry (LC/MS/MS) method with a validated quantification range for undiluted samples of 0.100–50 ng/mL whole blood (0.800 mL whole blood extracted). The 0.8 mL of whole blood was treated with 0.050 mL of a 200 ng/mL tacrolimus internal standard and 0.800 mL of zinc sulphate solution. After that 0.500 mL of ammonium acetate and 1.5 mL of acetone was added and samples were vortexed for 2 minutes. Samples were then centrifuged at 4000 rpm for 5 minutes at 10°C . After centrifugation supernatant was loaded on conditioned (1 mL of methanol followed by 1 mL of water) cartridges. Cartridge was washed with 1 mL of 10% acetic acid followed by 1 mL of 10% methanol. After that contents were eluted with 1 mL of acetonitrile and evaporated to dryness. Residue was then reconstituted with 100 μL of reconstitution solution. The reconstituted extract was chromatographed under reverse phase conditions on a Waters Acquity UPLC BEH C18, column using a gradient with organic mixture, and water containing ammonium acetate as the mobile phase solvents. The analyte and internal standard were detected and quantified by tandem mass spectrometry using electrospray ionisation. A linear function was fitted to calibration data using a $1/(\text{concentration})^2$ weighted least-squares regression.

Statistical methods for clinical results

Peak concentration (C_{max}) and time to C_{max} (T_{max}) were estimated directly from the data, and areas under the curve (AUC) were calculated by the linear trapezoidal rule. Pharmacokinetics variables were calculated by non-compartmental analysis (NCA) using WinNonlin® software version 5.3 (Pharsight Corporation, USA). The following pharmacokinetic parameters were calculated for each patient: T_{max} , time peak concentration occurs (h); C_{max} , peak blood concentration (ng/mL); AUC_{0-t} , area under the concentration-time curve from time zero up to the last quantifiable concentration (ng.h/mL); AUMC_{0-t} , area under the moment curve from the time of dosing (dosing time)

to the last measurable concentration (ng.h/mL); $\text{AUC}_{0-\text{inf}}$, area under the concentration-time curve from time zero and extrapolated to infinite time (ng.h/mL); $\text{AUMC}_{0-\text{inf}}$, area under the first moment curve (AUMC) extrapolated to infinity, based on the last observed concentration (ng.h/mL); $t_{1/2}$, terminal phase elimination half-life (h); CL, total blood clearance (L/h); mean residence time (MRT) from the time of dosing (dosing time) to the time of the last measurable concentration (AUMC/AUC) (h); $V_{d\text{area}}$, apparent volume of distribution in the terminal phase (L); λ_z (Kel), terminal phase rate constant, estimated from log-linear regression analysis of the terminal phase of the blood concentration-time profile. Summary data are presented as mean $\pm$ standard deviation (SD).

Results

Patient demographics

A total of 20 patients were included in the study and the total numbers of study stents implanted were 24. The mean age of the 20 patients was 54 ± 10 years; 15 (75%) of the 20 patients were male. Of the 20 patients, 5 (25%) patients had diabetes mellitus, 1 (5%) patient had hypercholesterolemia, and 9 (45%) patients were experiencing hypertension requiring medication. The location of the lesion was left anterior descending in 54%, left circumflex in 8% and right coronary artery in 38%. The patient characteristics are presented in Table 1.

Pharmacokinetic results

The individual sirolimus blood concentrations over time, with individual patient pharmacokinetic parameters presented in Figure 2 and Table 2 along with average pharmacokinetic

Table 1
Patient characteristics.

Patient characteristics	n=20 patients
Age (yr)	54 ± 10
Male, n (%)	15 (75)
Diabetes mellitus, n (%)	5 (25)
Insulin dependent, n (%)	2 (40)
Insulin non-dependent, n (%)	3 (60)
Current smoker, n (%)	2 (10)
Hypercholesterolemia, n (%)	1 (5)
Hypertension, n (%)	9 (45)
Family history of CAD, n (%)	1 (5)
Previous MI, n (%)	2 (10)
Clinical presentation	
Unstable angina, n (%)	17 (85)
Stable angina, n (%)	3 (15)
Target vessel	n=24 vessels
Right coronary artery, n (%)	9 (38)
Left circumflex, n (%)	2 (8)
Left anterior descending, n (%)	13 (54)

CAD: coronary artery disease, MI: myocardial infarction.

Figure 2 Individual whole blood sirolimus values over 336 hours from patients receiving one (red line), two (blue line), and three (green line) stents.

Table 2
Individual patient's pharmacokinetic values.

Patient's Id. no.	No. of stents	T_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{0-t} (ng.h/mL)	$AUMC_{0-t}$ (ng.h/mL)	AUC_{0-inf} (ng.h/mL)	$AUMC_{0-inf}$ (ng.h/mL)	CL	MRT	Vd_{area}
2	1	6	1.59	49	90.21	4183	101.89	6975.14	0.76	46	54
3	1	12	0.96	72	69.49	3707	86.50	8339.97	1.11	53	116
4	1	12	2.15	170	233.58	24,347	300.12	63,040.58	0.38	104	94
5	1	4	1.45	161	138.18	15,228	174.34	35,766.69	0.66	110	153
6	1	6	3.88	112	248.13	19,031	272.50	31,147.95	0.70	77	114
9	1	4	1.18	75	58.57	2940	72.34	6732.99	1.06	50	114
10	1	4	2.06	74	100.75	4954	124.19	11,387.90	0.93	49	99
11	1	1	1.74	121	137.40	12,370	156.37	22,048.89	0.61	90	107
12	1	6	2.02	71	108.59	5390	131.12	11,483.28	0.88	50	90
13	1	4	2.12	46	95.55	4134	109.01	7297.18	1.23	43	82
14	1	4	1.71	58	100.25	4858	115.27	8648.40	0.83	48	70
15	1	2	3.30	84	222.41	13,983	235.35	19,895.67	0.65	63	79
16	1	4	1.84	142	129.47	12,053	153.99	25,299.89	0.75	93	153
18	1	2	1.33	61	69.86	3678	84.61	7444.13	1.13	53	99
19	1	4	0.98	53	49.47	2460	58.34	4632.49	0.98	50	75
20	1	1	0.73	99	45.19	2628	64.08	8505.47	0.89	58	127
21	1	6	3.54	152	293.13	27,619	354.25	61,594.43	0.54	94	119
1	2	4	4.13	121	294.14	26,490	335.25	47,457.31	0.74	90	129
7	2	4	3.96	108	177.84	13,598	194.85	21,971.77	0.79	76	123
8	3	6	3.81	109	243.00	19,899	266.75	31,610.83	0.94	82	147
No. of stent 1	n	17	17	17	17	17	17	17	17	17	17
	Mean	4.82	1.92	94.14	128.84	9621.39	152.603	20,014.18	0.83	66.61	102.63
	SD	3.15	0.90	41.20	75.40	8025.18	87.830	18,425.90	0.23	22.80	27.15
	SE	0.76	0.22	9.99	18.29	1946.39	21.302	4468.94	0.06	5.53	6.59
No. of stent 2	n	2	2	2	2	2	2	2	2	2	2
	Mean	4	4.05	114.46	235.99	20,043.58	265.049	34,714.54	0.76	83.26	125.97
	SD	0	0.12	8.84	82.24	9115.93	99.273	18,021.00	0.03	9.61	4.79
	SE	0	0.09	6.25	58.15	6445.93	70.197	12,742.77	0.02	6.80	3.38
No. of stent 3	n	1	1	1	1	1	1	1	1	1	1
	Mean	6	3.81	108.99	243.00	19,899.34	266.747	31,610.83	0.94	81.89	147.37
All patients	n	20	20	20	20	20	20	20	20	20	20
	Mean	4.80	2.22	96.91	145.26	11,177.51	169.555	22,064.05	0.83	69.04	107.20
	SD	2.91	1.12	38.48	82.18	8547.10	93.429	18,121.84	0.21	21.86	27.62
	SE	0.65	0.25	8.60	18.38	1911.19	20.891	4052.17	0.05	4.89	6.18

$t_{1/2}$: terminal phase elimination half-time (hr), AUC_{0-t} : area under the concentration-time curve (AUC) to the last time point having a detectable sirolimus level (ng.h/mL), $AUMC_{0-t}$: AUC under the first moment curve to last time point with a detectable sirolimus level (ng.h/mL), AUC_{0-inf} : AUC total area under the concentration-time curve (ng.h/mL), $AUMC_{0-inf}$: total AUC under first moment curve (ng.h/mL), CL: apparent clearance from blood (L/hr), MRT: mean residence time (AUMC/AUC, hr), Vd_{area} : apparent volume of distribution in the terminal elimination phase (L). SD: standard deviation, SE: standard error.

Figure 3 Mean whole blood sirolimus levels from 10 minutes to 336 hours following Supralimus-Core® SES implantation.

Table 3

Total stent dose of sirolimus received by patients.

Total sirolimus dose on stent (μg)	57	77	96	115	134	153	153	192	249	250
No. of stents	1	1	1	1	1	1	2	1	2	3
No. of patients	2	2	4	5	1	1	1	2	1	1

values for patients receiving either one, two, or three stents, and for the combined patient population. Average values for sirolimus concentration over time can be found in Figure 3.

The average peak blood concentration for patients receiving two stents was about twice the concentration as was observed in patients receiving one stent (one stent, $1.92 \pm 0.90 \text{ ng/mL}$ vs. two stents, $4.05 \pm 0.12 \text{ ng/mL}$, $P < 0.05$). The T_{max} was 4.82 ± 3.15 vs. 4 ± 0 hour, $t_{1/2}$ was 94.14 ± 41.2 , and 114.46 ± 8.84 hour ($P < 0.05$), and clearance was 0.83 ± 0.23 and $0.76 \pm 0.03 \text{ L/hr}$ in patients treated with one or two stents, respectively. The total stent dose of sirolimus received by each patient is listed in Table 3.

Mean whole blood concentrations of sirolimus increased as the total stent dose of sirolimus increased. Figure 4 provides the mean whole blood concentration-time curves of sirolimus/tertile of total drug dose ($< 100 \mu\text{g}$, $100\text{--}200 \mu\text{g}$, and $> 200 \mu\text{g}$). For most patients, whole blood sirolimus concentrations initially increased to reach a maximum at about 2–8-hours after stent implantation. Thereafter, whole blood sirolimus concentrations decreased biphasically. An initially fast distribution/elimination phase was followed by a slower elimination phase.

The descriptive statistics/tertile of total drug dose ($< 100 \mu\text{g}$, $100\text{--}200 \mu\text{g}$, and $> 200 \mu\text{g}$) as shown in Table 4. The mean time to maximal whole blood concentrations was 4.25 ± 3.58 hours, 5.20 ± 2.70 hours, and 5.00 ± 1.41 hours for the first ($< 100 \mu\text{g}$), second ($100\text{--}200 \mu\text{g}$), and third tertile ($> 200 \mu\text{g}$) of the total drug

dose, respectively. The mean C_{max} values were $1.28 \pm 0.38 \text{ ng/mL}$, $2.63 \pm 0.93 \text{ ng/mL}$, and $3.97 \pm 0.23 \text{ ng/mL}$, respectively.

Discussion

The pharmacokinetic study was to determine the systemic exposure to sirolimus eluted from the Supralimus-Core® stent in the range of doses set by various size, length, and number of stents implanted in patients. Due to the involvement of so many factors, predictions and experimental assessment of the local pharmacokinetics in the case of stent-delivered drug appears to be much more difficult than in the case of systemic administration.

It is known that the pharmacokinetics of the eluted drug after DES implantation is different between systemic and tissue levels. The pharmacokinetic data in the present study showed that the Supralimus-Core® stent has a faster drug release rate compared with the Cypher stent.¹³ The maximum blood concentration of sirolimus occurred between 4 hours and 6 hours after implantation with a peak concentration of $1.92 \pm 0.90 \text{ ng/mL}$ (mean $\pm$ SD), $4.05 \pm 0.12 \text{ ng/mL}$, and 3.81 ng/mL in patients receiving one, two, or three Supralimus-Core® stents, respectively. While in Cypher SES maximum blood concentration of sirolimus occurred between 3 hours and 4 hours after implantation, with a peak concentration of

Figure 4 Mean $\pm$ standard deviation whole blood concentration-time curves of sirolimus, linear graph, for three groups of total drug dose (<100 μ g, 100–200 μ g, and >200 μ g).

Table 4

Pharmacokinetics of Supralimus-Core[®] sirolimus-eluting stents for three different dose groups.

	< 100 μ g	100–200 μ g	>200 μ g
N	8	10	2
T_{max} (h)	4.25 $\pm$ 3.58	5.20 $\pm$ 2.70	5.00 $\pm$ 1.41
C_{max} (ng/mL)	1.28 $\pm$ 0.38	2.63 $\pm$ 0.93	3.97 $\pm$ 0.23
AUC_{0-24} (ng.h/mL)	24.09 $\pm$ 7.66	49.20 $\pm$ 17.01	73.09 $\pm$ 4.56
AUC_{0-t} (ng.h/mL)	77.55 $\pm$ 30.65	174.76 $\pm$ 70.44	268.57 $\pm$ 36.16
AUC_{0-inf} (ng.h/mL)	92.42 $\pm$ 32.0	204.97 $\pm$ 82.76	300.99 $\pm$ 48.44
$t_{1/2}$ (h)	73.56 $\pm$ 24.69	112.0 $\pm$ 42.84	114.85 $\pm$ 8.29
CL (L/h)	0.92 $\pm$ 0.18	0.75 $\pm$ 0.23	0.84 $\pm$ 0.14

T_{max} , time peak concentration occurs (h), C_{max} , peak blood concentration (ng/mL), $t_{1/2}$, terminal phase elimination half-time (hr), AUC_{0-24} , AUC_{0-t} : area under the concentration-time curve (AUC) to the last time point having a detectable sirolimus level (ng.h/mL), AUC_{0-inf} : AUC total area under the concentration-time curve (ng.h/mL), CL: apparent clearance from blood (L/hr).

0.57 $\pm$ 0.12 ng/mL and 1.05 $\pm$ 0.39 ng/mL in patients receiving one or two stents, respectively.¹³ The higher concentration in Supralimus-Core[®] may be because of difference in polymers. In Supralimus-Core[®] biodegradable polymers used while in Cypher stent permanent polymers are used. The sirolimus AUC_{0-t} after implantation of a single Cypher stent was 55.13 $\pm$ 15.49 ng.h/mL, while in Supralimus-Core[®] stent after implantation of a single stent was 128.84 $\pm$ 75.40 ng.h/mL. The C_{max} and AUC are proportional to the dose in the range of 57–250 μ g following Supralimus-Core[®] stent implantation.

An interesting finding in the present study is that $t_{1/2}$ of 102 hours (pooled data for one, two, and three stents). This is considerably longer than the $t_{1/2}$ of ~60 hr reported after oral administration of sirolimus. Zimmerman and Kahan¹⁴ reported the oral sirolimus $t_{1/2}$ to range from 60–83 hour following oral doses ranging from 0.5–6.5 mg/m²/12 hour (mean $t_{1/2}$ for

all doses 62.3 hour). While Brattstrom et al.¹⁵ reported $t_{1/2}$ values ranging from 39 hours to 87 hours following oral doses ranging from 3 mg/m² to 15 mg/m² (mean $t_{1/2}$ for all doses 56.9 hours).

In the present study, patients who were treated with Supralimus-Core[®] stents had low, but measurable sirolimus blood levels for at least 7 days after deployment, with systemic exposure being proportional to the number of stents received.

The estimated clearance of sirolimus following stent deployment observed in the present study is similar to what has been previously reported in transplant patients receiving oral sirolimus. In a population pharmacokinetic reported by Zheng et al.¹⁶ 180 transplant patients and healthy subjects were studied. The average whole blood clearance was found to be 2.16 L/hr in a typical healthy individual, 35 years of age. This is comparable to the clearance estimates obtained following setting with one, two, and three stents in the present study of 0.83 L/hr, 0.76 L/hr, and 0.94 L/hr, respectively. The highest sirolimus blood concentration measured in all samples was 4.13 ng/mL. Continuous drug availability through prolonged drug release also most likely contributes to the prolonged clearance time.

The drug coating in multiple layers with the use of biodegradable layers for the Supralimus-Core[®] stent is designed to deliver the drug in a biphasic manner: an initial burst dose, followed by a controlled release of the drug which will likely reduce late adverse clinical events compared to stents with non-biodegradable polymer.

It is reasonable to expect that the low exposure to sirolimus is the reason for the good tolerability and safety profile in the current study, in which not a single case of sirolimus-related toxicity was observed.

Conclusion

In conclusion, this study confirms that the Supralimus-Core® stent causes only limited systemic exposure to sirolimus. In this study, sirolimus concentration in systemic circulation is to be safe, well-tolerated, and short-lived.

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