Pharmacokinetic analysis after implantation of everolimus-eluting self-expanding stents in the peripheral vasculature

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Background: **A novel self-expanding drug-eluting stent was designed to release everolimus 225 μg/cm² to prevent restenosis following peripheral arterial intervention. The purpose of this study was to measure the pharmacokinetic profile of everolimus following stent implantation.**

Methods: **One hundred four patients with symptomatic peripheral arterial disease underwent implantation of everolimus-eluting stents in the femoropopliteal arteries. In a prespecified subset of 26 patients, blood samples for assay of everolimus content were collected prior to stent implantation, at 1, 4, and 8 hours postprocedure, prior to discharge, and at 1 month postprocedure.**

Results: **A total of 39 stents, ranging from 28 mm to 100 mm in length, were implanted in 26 patients, resulting in a total delivered everolimus dose range of 3.0 to 7.6 mg. Following the procedure, the maximum observed everolimus blood concentrations (C_{max}) varied from 1.83 ± 0.05 ng/mL after implantation of a single 80-mm stent to 4.66 ± 1.78 ng/mL after implantation of two 100-mm stents. The mean time to peak concentration (T_{max}) varied from 6.8 hours to 35 hours. The pharmacokinetics of everolimus were dose-proportional in that dose-normalized C_{max} and area under the curve values were constant over the studied dose range.**

Conclusions: **After implantation of everolimus-eluting self-expanding stents in the femoropopliteal arteries, systemic blood concentrations of everolimus are predictable and considerably lower than blood concentrations observed following safe oral administration of everolimus. (J Vasc Surg 2012;55:400-5.)**

Intracoronary stents that elute either sirolimus (rapamycin), paclitaxel, everolimus, or zotarolimus have each been shown to effectively inhibit restenosis in large-scale clinical trials.[1] Their inhibitory effect on restenosis has been profound, consistently reducing the need for repeat intervention by ≥50% as compared with bare metal stents.[2,3] Although a variety of designs are available, each with their own unique combination of device, drug, and polymer, the relatively small size of coronary drug-eluting stents (DES) assures that their total drug content rarely exceeds 0.2 mg. This small dose seldom results in substantial systemic exposure to the patient; indeed, pharmacokinetic (PK) studies of patients treated with coronary DES reveal that the maximum systemic drug concentration observed is typically <2 ng/mL, far below accepted limits of pharmacologic safety for these compounds.[4,5]

Although efficacious in the coronary vasculature, the concept of stent-based drug elution to prevent restenosis has not been successfully adapted to the peripheral arteries. The arteries of the periphery, most notably the superficial femoral artery (SFA), are long and tortuous, with heavy and complex plaque burdens typically characterized by multiple serial stenoses and occlusions. Compared with the coronary arteries, therefore, intravascular devices designed for the SFA must be larger, longer, and considerably more flexible. They must, by necessity, contain much greater total drug content.

In the SFA TReatment with Drug-Eluting Stents, (STRIDES) clinical trial, a novel self-expanding nitinol drug-eluting stent system was designed to slowly release everolimus 225 μg/cm² over a period of several months. The relatively large diameter and long length of the stent necessitated high total drug loads, ~4 mg in the longest device. The clinical results of the STRIDES trial have been published elsewhere.[6] The purpose of this study

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Trial Registration: Clinicaltrials.gov; identifier: NCT00475566.

Competition of interest: Drs Lammer and Scheinert serve on the Advisory Board of Abbott Vascular; Dr Lammer serves on the Steering Committee of the STRIDES trial; Drs Lammer and Vermassen receive research support from Abbott Laboratories; and Drs Menon and Schwartz are all full-time employees of Abbott Laboratories.

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was to measure the human PK profile of everolimus up to 1 month following peripheral vascular implantation.

METHODS

Study design and endpoints. The STRIDES trial was a prospective, nonrandomized, single-arm, multicenter clinical study designed to evaluate the safety and performance of an everolimus-eluting peripheral stent system for the treatment of atherosclerotic peripheral arterial disease (PAD). The study was designed to enroll approximately 100 patients with chronic PAD in Rutherford Becker Clinical Categories 2–5 (moderate to severe intermittent claudication, ischemic rest pain, or ischemic ulceration) due to atherosclerotic de novo or restenotic occlusive lesions of the SFA or proximal popliteal artery ≥3 and ≤17 cm in length. Stents were available in 28-, 80-, and 100-mm lengths; the maximum allowable stent length per patient was 200 mm. Key exclusion criteria included the presence of an active immunosuppressive disorder, active pharmacologic treatment with known inducers of CYP3A, prior or planned solid organ transplantation, severe hepatic insufficiency, or renal insufficiency defined by a serum creatinine >2.5 mg/dL.

In order to assess the human PK profile after everolimus-eluting self-expanding stent implantation, a subset of clinical sites were selected to participate in a PK substudy of STRIDES. This substudy is the subject of this article.

The STRIDES PK substudy was conducted in accordance with the International Conference on Harmonization (ICH) guidelines-Good Clinical Practices (GCP), Declaration of Helsinki, ISO 14155-1, ISO 14155-2, and Ethics Committee requirements. All patients gave written informed consent for participation.

Drug-eluting stent system. The everolimus-eluting peripheral stent system is comprised of three components: the DYNALINK nitinol self-expanding stent, the antiproliferative drug everolimus, and an ethylene vinyl alcohol (EVAL; Kuraray Co, LTD, Osaka, Japan) copolymer.

The DYNALINK .035 Peripheral Self-Expanding Stent (Abbott Laboratories, Abbott Park, Ill) is constructed of binary nickel-titanium, which is superelastic at body temperature. The 0.008-inch strut thickness design is based on a series of sinusoidal rings that are connected at six locations around the circumference such that the connections are aligned along the length of the stent and positioned 60 degrees from each other. The safety and efficacy of the stent system has been examined in several single-arm and randomized trials of endovascular therapy of PAD.[7-11]

The antiproliferative drug, everolimus (40-O-(2-hydroxyethyl)-rapamycin), is a therapeutic agent originally developed for the prevention of organ transplant rejection but is also effective at inhibiting the growth of many solid tumors (CERTICAN, ZORTRESS, AFINITOR; NOVARTIS Pharmaceuticals Corporation, Basel, Switzerland).[12-16] It is a macrolide derivative of rapamycin (sirolimus) that forms a complex with the cyclophilin FKBP-12, which binds and inactivates the serine–threonine kinase mammalian target of rapamycin (mTOR). This complex, known as mTORC1, inhibits ribosomal S6 kinase-1 (S6K1) and the mRNA cap-binding protein eIF4E, which are required for efficient translation of certain cell cycle regulators such as cyclin D1 and ornithine decarboxylase as well as transcription factors such as c-MYC and HIF-1α.[16] Without these transcription signals, the cell is unable to transit from the G1 to S phase, so it is statically arrested.

Oral everolimus is rapidly absorbed with peak concentrations achieved in 1 to 2 hours and steady states generated after ~4 days.[17] The human half-life and volumes of distribution are 24 to 35 hours and ~110 L, respectively.[12,18] Pharmacologically, everolimus has been shown to be safe and well-tolerated at systemic therapeutic concentrations between 3 and 15 ng/mL.[18-20] Approximately 98% of the drug is metabolized in the liver, so everolimus should be dosed cautiously in patients with hepatic dysfunction.[21]

Pharmacodynamically, everolimus inhibits vascular smooth muscle cell proliferation, enhances vascular remodeling,[13,22,23] and has been shown to be safe and effective as the drug component of coronary DES.[24,25] In the peripheral stent system tested herein, the elution of everolimus was controlled by an EVAL copolymer. EVAL is a semicrystalline polymer with a glass transition temperature (T_g) of 55°C and melting point (T_m) of 180°C. The chemical backbone is a C–C bond, and the pendant group is –OH; neither contains hydrolytically or oxidatively labile chemical bonds. Owing to their biocompatibility, EVAL polymers are ubiquitous in medicine. They have been used as hemodialysis and apheresis membranes[26-28] and have been formulated with dimethyl sulfoxide (DMSO) for use as embolic treatment for intracerebral aneurysms and arteriovenous malformations.[29-32]

This combination of the DYNALINK nitinol self-expanding stent, the antiproliferative drug everolimus, and an EVAL copolymer has been referred to as the "DYNALINK-E" stent. The total drug load is 225 μg/cm² stent surface area, a higher dose than coronary sirolimus-eluting (140 μg/cm²) or coronary everolimus-eluting stents (100 μg/cm²).[25,33] The elution profile is prolonged, with approximately 80% of the drug being released slowly over the first 90 days,[34] as opposed to only 30 days in most systems designed for use in the coronary arteries. For the STRIDES trial, the stent was available in lengths of 28, 80, and 100 mm, with diameters of 6 or 8 mm. Given the nominal drug loading specification of 225 μg/cm² stent surface area, and the allowable total stent length range of 80 to 200 mm, the total delivered everolimus dose ranged from 3.0 to 7.6 mg per patient.

Blood sample collection and disposition. Blood samples for everolimus assay were collected by venipuncture into 4-mL potassium edetic acid (EDTA) vacutainers. Samples were obtained prior to stent implantation (0 hr), at approximately 1, 4, and 8 hours after final stent placement, before subject discharge (collection times ranged from 17-166 hours), and at 1 month after discharge from the study site. A total of six blood samples per patient were to be collected for pharmacokinetic analysis. The frozen blood samples were shipped from the study site to Eurofins Medi-

Table I. Clinical demographics of the 26 patients enrolled in the pharmacokinetic subset of the STRIDES trial

Demographics	*Mean ± SD or % of patients*
Age (years)	67 ± 11
Male gender	69%
Current or former smoker	77%
Diabetes mellitus	50%
Hypertension	81%
Hypercholesterolemia	88%
Coronary artery disease	58%
Contralateral peripheral vascular disease	77%
Limb salvage indication	15%

net BV (Breda, the Netherlands) for analysis of everolimus. Samples were stored frozen at approximately -20°C until analyzed; a maximum of 260 days elapsed between collection and analysis, which was within the documented 1-year stability for everolimus in frozen blood samples.

Whole blood concentration of everolimus was determined using a validated liquid/liquid extraction high-performance liquid chromatography (HPLC) method with tandem mass spectrometric detection (LC-MS/MS). Acomycin was used as an internal standard. The lower limit of quantitation (LLOQ) for everolimus was 0.2 ng/mL using a 0.020-mL blood sample. Samples quantified below the lowest standard were reported as zero. In-study quality control (QC) samples, supplemented with various concentrations of everolimus, were analyzed along with the unknowns.

Pharmacokinetic modeling and calculations. Individual blood concentrations and the PK parameter values of everolimus were tabulated for each individual by dose group. PK parameter values of everolimus were estimated using noncompartmental methods and the actual sampling times. These included the maximum observed plasma concentration (C_{max}) and time to C_{max} (T_{max}), and the area under the plasma concentration-time curve (AUC) from time 0 to 24 hours ($AUC_{0\text{-}24}$) and to the time of the last measurable concentration ($AUC_{0\text{-last}}$). AUC was calculated by linear trapezoidal rule. Dose-normalized C_{max} and AUC values were calculated algebraically by dividing the PK parameter with the nominal dose. Winnonlin Professional software (version 5.5; PHARSIGHT Corporation, Mountain View, Calif) was used for calculation of PK parameters. Data are expressed as mean ± standard deviation unless otherwise noted.

RESULTS

Twenty-six patients were sequentially enrolled from seven clinical sites in Europe. Their clinical demographics are given in Table I and are typical for patients with end-stage PAD. Most lesions were de novo in nature, although a single patient with restenosis was treated. The mean lesion length was 9.0 ± 4.4 cm (range, 3.0-17.0 cm); 46% of lesions were totally occluded at the time of intervention.

A total of 39 stents were implanted in 26 patients. A retrospective evaluation of the stent combinations deployed revealed six unique dose groups, with total implanted stent length ranging from 80 to 200 mm (Table II). This corresponded to a total everolimus dose range of 3.0 to 7.6 mg.

The mean blood concentration-time profiles for all dose groups (I through VI) are given in Fig 1. Everolimus release began immediately after stent implantation as evidenced by the appearance of quantifiable whole blood concentrations after 1 hour, the first time point measured. The mean everolimus concentrations generally increased with increasing dose and remained relatively flat over the first 24 hours. As expected from the polymer design, the highest whole blood everolimus levels were generally observed within the first day, although everolimus remained detectable in most patients even at 30 days.

Calculated PK parameters for the various doses administered are provided in Table III. The C_{max} varied from 1.83 ± 0.05 ng/mL after implantation of a single 80-mm stent to 4.66 ± 1.78 ng/mL after implantation of two overlapping 100-mm stents. The $AUC_{0\text{-last}}$ varied from 50 to 2000 ng · h/mL. The PKs of everolimus were essentially linear, as illustrated by the relatively similar dose-normalized C_{max} and AUC values over the studied dose range (Fig 2).

DISCUSSION

Given the success of DES at preventing restenosis in the coronary arteries, many have theorized that this technology might also be useful in the peripheral arteries.[35-38] The sirolimus-coated self-expanding SMART stent (Cordis, a Johnson & Johnson Company, Miami Lakes, Fla) remains the first, and only, peripheral drug-eluting stent to be tested in clinical trials and reported in the literature.[35,39] This device utilized the nitinol SMART stent as its platform, was loaded with 90-μg sirolimus/cm^2 stent area using a 5- to 10-μm copolymer matrix, and delivered its ~1-mg drug load (per 80-mm stent) over a period of about 7 days. A total of 93 patients were enrolled in the combined SIROCCO I and SIROCCO II clinical trials (SIROlimus Coated COrdis SMART nitinol self-expandable stent for the treatment of obstructive superficial femoral artery disease). Unfortunately, neither trial achieved its primary endpoint of a reduction in restenosis and, even after 4 years, there was no difference in any metric comparing patients treated with the bare SMART stent versus the sirolimus-eluting stent.[38]

Despite the disappointing results of the SIROCCO studies, two other peripheral DES are currently being tested in clinical trials. The ZILVER PTX stent (Cook Incorporated, Bloomington, Ind) is loaded with approximately 300 μg paclitaxel/cm^2 stent area.[40] Similar to the ACHIEVE coronary stent (Cook) tested in the DELIVER clinical trial (the RX ACHIEVE drug-eluting coronary stent system in the treatment of patients with De noVo cativE coronaRy lesions),[41] paclitaxel is applied directly to the ZILVER PTX stent; there is no polymer system serving

Table II. Dosing scheme of patients enrolled in pharmacokinetic subset of the STRIDES trial

Dose group	*Number of patients*	*Stent sizes implanted*	*Total stent length*	*Total everolimus dose (μg)*
I	3	80 mm	80 mm	3033
II	10	100 mm	100 mm	3777
III	1	28 mm + 100 mm	128 mm	4847
IV	2	80 mm + 80 mm	160 mm	6066
V	4	80 mm + 100 mm	180 mm	6810
VI	6	100 mm + 100 mm	200 mm	7554

Total stent length represented as length of first stent + length of second stent.

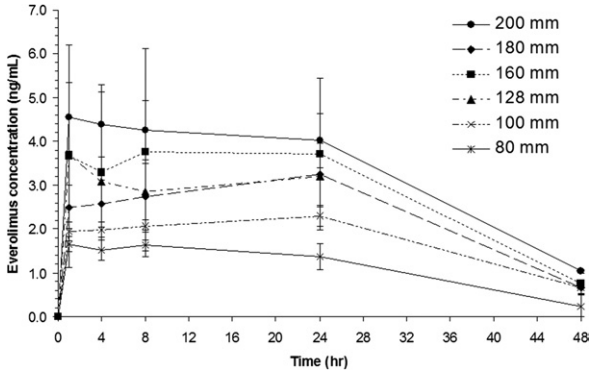

Fig 1. Mean everolimus blood concentration-time profiles after self-expanding everolimus-eluting stent implantation. Note the nonlinear nature of the time scale. Data points represent mean ± standard error.

to control its release. Clinical trial results have not yet been made available in the scientific literature.

Lastly, an everolimus-eluting nitinol stent has also recently undergone clinical testing and is the subject of this report. The DYNALINK-E device contains approximately 225 μg everolimus/cm^2 stent area, which is released slowly through its incorporation in an EVAL copolymer. The DYNALINK-E stent was tested clinically in the STRIDES trial, a prospective, nonrandomized, single-arm, multicenter clinical study designed to evaluate the safety and performance of this stent system in patients with atherosclerotic or restenotic PAD. The clinical results of the STRIDES trial have been published elsewhere.[6] The purpose of this communication is to describe the PK results of STRIDES.

Following the implantation of DYNALINK-E, the maximum observed everolimus blood concentration (C_{max}) varied from 1.83 ± 0.05 ng/mL after placement of a single 80-mm stent to 4.66 ± 1.78 ng/mL after placement of two overlapping 100-mm stents. The mean time to peak concentration (T_{max}) varied from 6.8 hours to 35 hours. The PK profiles of everolimus released from the stent were essentially linear, as illustrated by the relatively similar dose-normalized C_{max} and AUC values over the studied dose range (Fig 2). This is an important safety feature of drug-eluting systems, that systemic drug concentrations are predictable and increase in proportion to the total stent length implanted.

Despite the fact that the peripheral DYNALINK-E stent contains more than 10 times the amount of drug as smaller coronary DES, the slow elution profile of DYNALINK-E assured that the maximal systemic drug concentrations remained modest. For example, the PK profiles of the sirolimus-eluting CYPHER stent (Cordis, Johnson and Johnson; Miami, Fla) were studied in 19 patients and reported in 2006.[4] The observed C_{max} after single CYPHER stent implantation was 0.57 ± 0.12 ng/mL, which increased to 1.05 ± 0.39 ng/mL after implantation of two stents. This range is only slightly lower than the range reported herein for the DYNALINK-E stent (1.83-4.66 ng/mL). Similarly, PK results after implantation of the everolimus-eluting XIENCE V coronary stent (Abbott) are also available.[5] The XIENCE V stent is loaded with everolimus 100 μg/cm^2 stent area, somewhat lower than the sirolimus dose on CYPHER (140 μg/cm^2) and considerably less than DYNALINK-E (225 μg/cm^2). In the XIENCE V PK trial, 39 patients received XIENCE V stents, resulting in a total everolimus dose range of 53 to 588 μg. Mean C_{max} values ranged from 0.41 ± 0.16 ng/mL (for total stent dose <100 μg) to 0.72 ± 0.34 ng/mL (100-200 μg total dose) to 1.43 ± 0.58 ng/mL (>200 μg total dose).

Although everolimus C_{max} values for patients treated with DYNALINK-E are quantitatively similar to everolimus and sirolimus concentrations in patients treated with coronary DES, the high drug content and slow elution of DYNALINK-E naturally resulted in a more sustained systemic PK profile. This was evident in that everolimus could be detected in low concentrations (<1 ng/mL) in most patients even at the 30-day time point, and the AUC values for DYNALINK-E far exceeded coronary DES profiles (DYANLINK-E range 50-2000 ng · h/mL compared with the XIENCE V stent 19-85 ng · h/mL). This was a key design feature of DYNALINK-E, that the high total drug load would be released slowly, resulting in sustained but relatively low systemic concentrations.

Furthermore, the observed peak exposure of everolimus following implantation of DYNALINK-E stents was well below peak concentrations observed in safety studies of oral everolimus therapy. For example, Neumayer et al treated cadaveric renal transplant recipients receiving cyclosporine A with everolimus in single oral doses ranging from 0.25 to 25 mg.[42] Peak concentrations ranging from 2.3 ± 0.8 to 179 ± 24 ng/mL were observed, and all dose levels

Table III. Calculated pharmacokinetic parameters of patients enrolled in pharmacokinetic subset of the STRIDES trial

Pharmacokinetic parameter	*Group I (3.0 mg) n = 3*	*Group II (3.8 mg) n = 10*	*Group III (4.8 mg) n = 1*	*Group IV (6.1 mg) n = 2*	*Group V (6.8 mg) n = 4*	*Group VI (7.6 mg) n = 6*
Total stent length	80 mm	100 mm	128 mm	160 mm	180 mm	200 mm
C_{max} (ng/mL)	1.83 ± 0.05	2.44 ± 0.61	3.70	4.09 ± 2.98	3.35 ± 1.30	4.66 ± 1.78
C_{max}/dose (ng/mL/mg)	0.60 ± 0.02	0.65 ± 0.16	0.76	0.67 ± 0.49	0.49 ± 0.19	0.62 ± 0.24
T_{max} (h)	18.26 ± 20.02	22.75 ± 22.63	1.02	34.40 ± 47.24	35.44 ± 40.19	6.85 ± 9.44
$AUC_{0\text{-}24}$ (ng · h/mL)	36.31 ± 4.76	48.12 ± 13.39	[a]	84.60 ± 73.16	49.05 ± 9.75	74.24 ± 60.01
$AUC_{0\text{-}24}$/dose (ng · h/mL/μg)	11.97 ± 1.57	12.74 ± 3.55	[a]	13.95 ± 12.06	7.20 ± 1.43	9.83 ± 7.94
$AUC_{0\text{-}last}$ (ng · h/mL)	308.42 ± 293.5	975.9 ± 501.2	56.6[b]	1997.3 ± 1389.3	1571.96 ± 752.1	1422.88 ± 840.2
$AUC_{0\text{-}last}$/dose (ng · h/mL/μg)	101.69 ± 96.77	258.38 ± 132.68	11.67[b]	329.26 ± 229.03	230.83 ± 110.44	188.36 ± 111.22

$AUC_{0\text{-}24}$, Area under the plasma concentration-time curve from time 0 to 24 hours; $AUC_{0\text{-}last}$, area under the plasma concentration time-curve to the time of the last measurable concentration; C_{max}, maximum observed everolimus blood concentrations; T_{max}, mean time to peak concentration.
[a]Not determined as the last sample time point was 19 hours in these patients.
[b]The last sample time point was 19 hours in this patient as compared with ~30 days for most others.

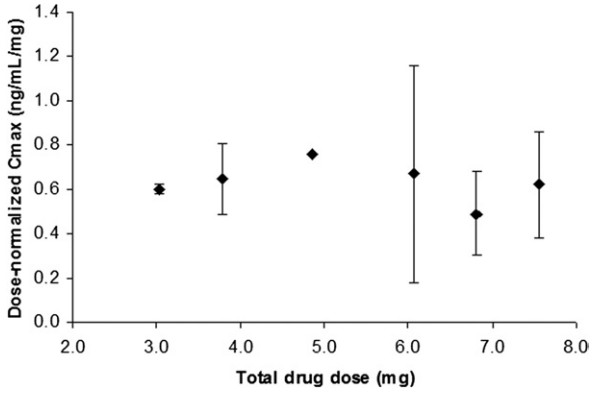

Fig 2. Dose-normalized C_{max} versus total everolimus dose in the STRIDES pharmacokinetic substudy. Treatment with DYANLINK-E resulted in approximately 0.6 ng/mL whole blood concentration per mg of stent-based everolimus implanted. Data points represent mean ± standard deviation.

were well-tolerated. In a longer-term study, Budde et al treated a similar patient population with oral everolimus in doses of 0.75 to 10 mg per day for 4 weeks and documented similar C_{max} ranges of 22 to 169 ng/mL.[19] Lastly, Kovarik et al followed 101 patients receiving daily everolimus in divided doses of 1 to 4 mg for a full year and documented steady state C_{max} levels ranging from 5 to 22 ng/mL.[20] Even when combined with other immunosuppressants in this difficult patient population, adverse events such as transient thrombocytopenia and leukopenia were uncommon. As a result, oral everolimus is available worldwide as an immunosuppressive adjunct for the prevention of rejection of transplanted solid organs (Certican, Zortress) and, recently, has been approved in the United States (Afinitor) as adjunctive chemotherapy for advanced renal cell carcinoma,[43,44] advanced pancreatic neuroendocrine tumors,[45] and subependymal astrocytoma associated with tuberous sclerosis.[46]

In summary, despite the relatively high drug loads contained within the DYNALINK-E everolimus-eluting peripheral self-expanding stent, its implantation is well-tolerated and generates a systemic PK profile well below the maximum observed whole blood concentrations following oral everolimus administration.

AUTHOR CONTRIBUTIONS

Conception and design: JL, RM, LS
Analysis and interpretation: JL, RM, LS
Data collection: JL, DS, FV, RK, KH, HS, RM, LS
Writing the article: JL, RM, LS
Critical revision of the article: JL, DS, FV, RK, KH, HS, RM, LS
Final approval of the article: JL, DS, FV, RK, KH, HS, RM, LS
Statistical analysis: JL, RM, LS
Obtained funding: LS
Overall responsibility: JL, LS

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