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**PRECLINICAL AND CLINICAL EVALUATION
OF A NOVEL SYNTHETIC BIORESORBABLE, ON-DEMAND,
LIGHT-ACTIVATED SEALANT IN VASCULAR RECONSTRUCTION**

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ORIGINAL ARTICLE

VASCULAR SURGERY

Preclinical and clinical evaluation of a novel synthetic bioresorbable, on-demand, light-activated sealant in vascular reconstruction

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ABSTRACT

BACKGROUND: Synthetic vascular material use, particularly polytetrafluoroethylene- (PTFE) -based, can be associated with bleeding, which may increase operative time and blood loss. None of the commercially available sealants designed to ensure hemostasis combine bioresorption, high viscosity, hydrophobicity, and compliance with the underlying tissue and on-demand activation.
METHODS: A study was designed to assess the biocompatibility and in-vivo performance and bioresorption of a new synthetic on-demand light-activated poly(glycerol-sebacate) acrylate- (PGSA) -based SETALIUM™ Vascular Sealant (TISSIUM, Paris, France) in three large animal studies of open vascular carotid and aortic surgery. The pre-clinical results were then translated into a clinical setting in a prospective, single-arm multicenter study in patients requiring carotid endarterectomy using an ePTFE patch.
RESULTS: The biocompatibility testing showed that the PGSA-based SETALIUM™ Vascular Sealant did not induce any significant toxic reaction at a standard clinical dose nor at doses up to 40 times the equivalent intended clinical dose. The PGSA-based sealant was shown to be non-pyrogenic, non-sensitizing, non-irritant, non-clastogenic, and non-mutagenic. The animal studies showed excellent performance and safety results, with clinically significant hemostasis achieved in 100% of the animals in both carotid and aorta studies and excellent local tolerance. Histopathology and morphometric analyses showed surface-based gradual and sustained bioresorption of the PGSA-based sealant up to 86% at 12 months. In the clinical study, the application of the PGSA-based sealant resulted in good performance and safety, with immediate hemostasis achieved in 84% of the cases and no adverse event related to the sealant reported through the one-year follow-up.
CONCLUSIONS: The new synthetic on-demand light activated PGSA-based SETALIUM™ Vascular Sealant investigated in our studies demonstrated good biocompatibility, sustained and gradual surface based bioresorption, and acceptable safety profile in animal studies. In addition, the first in-human use showed that the sealant is a safe and effective alternative to achieve fast and controlled hemostasis in vascular carotid reconstructions. A larger randomized controlled study will allow further validation of these encouraging preliminary results.

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Key words: Polymers; Vascular surgical procedures; Biocompatible materials; Materials testing; Poly(glycerol-sebacate).

Fast and efficient hemostasis is a fundamental component of vascular surgery and is a critical element of success in vascular reconstructions. The high prevalence of anticoagulant and antiplatelet agent use among patients undergoing vascular surgical procedures along with intraoperative heparin administration may contribute to acute

coagulopathy with significant blood loss.[1] In addition, the use of synthetic vascular materials, particularly polytetrafluoroethylene- (PTFE) -based ones, is often associated with bleeding through suture holes, and associated increased operative times and blood loss.[2] The use of sealant in selected groups may confer considerable economic benefits to hospital and health service budget.[3] In this context, a wide variety of solutions such as hemostatic agents, sealants, and adhesives are currently available on the market, but all have potential shortcomings.[4]

Although commonly used, fibrin-based sealants are not universally considered as the standard of care hemostatic adjunct in vascular surgery.[5] Fibrin sealants have several disadvantages, including low adhesive strength, high costs, and possible virus transmission as fibrin products are usually made from plasma pooled from human donors.[6]

Cyanoacrylate-based sealants have acceptable adhesion properties on many different substrates, however they typically polymerize very quickly prior to tissue contact. Their viscosity is low before polymerization, thereby increasing the risk of unintentional application on non-targeted tissues and organs, and the polymer becomes a non-elastic brittle material when polymerize.[7, 8] In addition, cyanoacrylate sealants generate toxic volatile compounds during application, creating safety issues for users, and are degraded into cyanoacetate and formaldehyde compounds, inducing tissue necrosis and a chronic inflammation process at the application site.[9, 10] Among the commercially available adhesives based on albumin and aldehyde compounds, polyethylene glycol (PEG) -based sealants (DuraSeal, Integra Lifescience, Plainsboro, NJ, USA; Coseal, Baxter Healthcare Corp., Westlake Village, CA, USA; VascuSeal, Covidien, Mansfield, MA, USA) have low bond strength and therefore can be easily washed away in a wet and dynamic environment. PEG-based sealants are fully synthetic materials with high swelling property which can induce a local compression of organs therefore increasing risk of necrosis of the surrounding organs.[11, 12]

In summary, none of the commercially available sealants fully addresses all the requirements to yield a vascular sealant that can function well in a wet environment.

The new poly(glycerol-sebacate) acrylate- (PGSA) -based sealant SETALIUM™ Vascular Sealant (TISSIUM, Paris, France) is a synthetic polymer platform that has been engineered as an optimal hemostatic adjunct to suturing during open vascular surgery. Prior to activation, the material is viscous and hydrophobic, enabling a precise application with minimum washout, even in the presence of body fluids. Once applied as a thin homogenous layer on tissue, it can be activated on-demand using light yielding a hermetic and elastic barrier by mechanical interlocking with the tissue surface.[13] The sealant bioresorbs by a surface erosion mechanism through hydrolysis without disrupting the healing process.[14, 15] Furthermore, the sealant is not biologically derived, obviating the possibility of viral transmission that exists with fibrin sealants. Preclinical work has been conducted to assess the material for closure of ventricular defects and has explored its use for multiple indications.[13, 16]

In the studies described herein, the biocompatibility, in-vivo performance, and bioresorption of the new PGSA-based sealant SETALIUM™ Vascular Sealant were assessed in three large ovine animal studies of open vascular carotid and aortic surgery and then in a first-in-human safety and performance study in patients undergoing carotid reconstruction.

Materials and methods

The PGSA-based sealant

The PGSA-based synthetic SETALIUM™ Vascular Sealant (SVS) has been designed to achieve adhesion in wet dynamic environments with bioresorption, compliance with the underlying tissues, and on-demand activation. The polymer is amenable to precise application to tissue in-situ given its high viscosity and hydrophobicity. The sealant contains a specific photoinitiator allowing its fast polymerization (30 s/cm²) when using a proprietary light activation pen to provide an instant hermetic barrier. The LED intensity and wavelength (405 nm) were chosen to eliminate risks of tissue damage both to the patient (vascular tissue) and to the operator (eyes), therefore requiring no shielding during its use (Figure 1). The proprietary SETALIUM™ Light is a re-usable and non-sterile LED light pen protected by a dedicated sterile single-use sleeve before the polymerization. The light source is placed at 1 to 2 cm from the area to be polymerized.
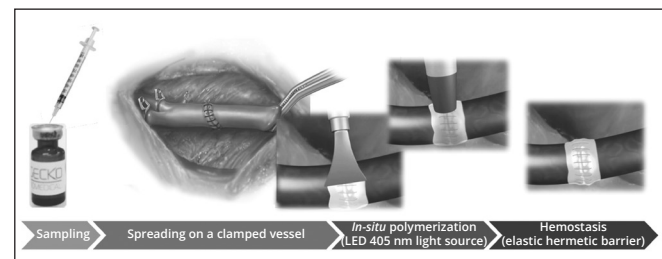

Figure 1.—Scheme of the *in-situ* use of the sealant.

In-vivo preclinical studies

All research procedures and maintenance, handling, anesthesia and euthanasia of animals during the entire study periods were conducted in compliance with ISO 10993-2 standard and the recommendations of the local Animal Care and Use Committee of the animal facility according to French government law on animal experimentation and European Convention of the Council of Europe.

Biocompatibility evaluation

Biocompatibility testing was performed in compliance with ISO 10993-1 standard and Good Laboratory Practices (GLP). The cytotoxicity, irritation, sensitization, acute systemic toxicity, hemocompatibility, pyrogenicity and genotoxicity of the sealant extracts were evaluated, and the general toxicity and local tolerance were assessed in a rat model following a subacute, subchronic, and chronic subcutaneous implantation (40 times the equivalent of the intended clinical dose). The methods used complied with the related standards (Table I).

In-vivo *performance and bioresorption evaluation*

CAROTID STUDIES

Two carotid studies were performed.

In carotid study 1, ten female sheep with a mean weight of 54 kg (range: 51-58 kg) were used. All the animals were pre-medicated at least 15 minutes before the surgical procedure (morphine 0.2 mg/kg, midazolan 0.5 mg/kg IM) and then anaesthetized (induction: sodium thiopental 5 to 10 mg/kg IV; maintenance: isoflurane 1-2%

TABLE I.—*List of performed biocompatibility studies under GLP conditions with related conditions.*

Study type (ISO part)	Study	Species/ Strain	Tested product	Ratio/dose	Result
Cytotoxicity (ISO 10993-5:2009)	Evaluation of cytotoxicity using an extract	Cells / Balb/c 3T3 clone A31	Extract, NaCl	6 cm²/mL	At a clinical equivalent dose, no cytotoxicity and no modification of cell density and cell morphology in comparison to negative control
Sensitization (ISO 10993-10:2010)	Assessment of sensitizing properties on albino Guinea pigs	10 albino Guinea pigs	Extract, polar and non-polar solvents	6 cm²/mL	No macroscopic cutaneous reaction attributable to allergy was recorded during the study in groups with polar and non-polar solvents. The sealant product is considered aa non-sensitizer
Intracutaneous irritation (ISO 10993-10:2010)	Assessment of local responses in the rabbit following intracutaneous injection	2×3 albino New Zealand rabbits	Extract, polar and non-polar solvents	6 cm²/mL	No cutaneous reactions were observed during the study following injection with polar and non-polar solvents. The sealant product is considered a non-irritant
Acute systemic toxicity (ISO 10993-11:2006)	Evaluation of acute toxicity in mouse following intraperitoneal injection	Swiss male mice, 4 groups of 5 animals (2 treated, 2 control)	Extract, polar and non-polar solvents	6 cm²/mL	No mortality occurred during the study. No clinical signs related to the administration with polar and non-polar extracts. The sealant product does not induce acute toxicity
Pyrogenicity (ISO 10993-11:2006)	Assessment of pyrogenicity in the rabbit following intra-venous injection	3 albino New Zealand rabbits	Extract, NaCl	6 cm²/mL	The maximal temperature rise of each animal was 0.05 °C with a total maximal temperature (N.=3) of 0.05 °C. The sealant product is considered non-pyrogenic
Genotoxicity (ISO 10993-3:2014)	Bacterial reverse mutation test: *Salmonella typhimurium* and *Escherichia coli*	*Salmonella typhimurium* TA98-1537-100-1535 *Escherichia coli* WP2 (uvr A) (pKM101)	Extract, polar and non-polar solvents	6 cm²/mL	There is no evidence of any increase in the number of revertant colonies in the presence of the sealant extracts (polar or non-polar), whatever the dilution, the bacterial strain and with or without activation. The PGSA-based sealant product is considered non-mutagenic
	In-vitro mammalian chromosome aberration test	Human lymphocyte cultures	Extract, polar and non-polar solvents	6 cm²/mL, with (15%) or without serum	No increase of chromosomal aberration and no increase of polyploidy and endoreduplication are observed whatever the conditions (assay 1 or assay 2) using the non-cytotoxic related dilutions. The sealant product is considered non-clastogenic

(To be continued)

TABLE I.—*List of performed biocompatibility studies under GLP conditions with related conditions (continues).*

Study type (ISO part)	Study	Species/ Strain	Tested product	Ratio/dose	Result
Hemocompatibility (ISO 10993-4:2002/ AM1:2006)	Hemolysis test	3 samples of citrate anticoagulated human blood	Extract, NaCl	6 cm²/mL	No hemolytic properties have been observed, *i.e.* no statistical difference from the negative control. The sealant product does not induce hemolysis
	Partial thromboplastin time	Whole human blood	Direct contact	3 cm²/mL, thickness <0.5 mm	The clotting time of the test item is not different from the clotting time of the negative control (225±32.8 s and 209.1±8.0 s, respectively). The sealant product is a non-activator of the intrinsic coagulation pathway
	Human complement system activation	2 pools of normal human serum			No modification of CH50 significantly, demonstrating the lack of complement consumption, and no modification of SC5b-9 level. The sealant product does not induce human complement activation
Local effect and systemic toxicity (ISO 10993-6:2009, ISO 10993-11:2009)	Subacute toxicity study with non-polymerized product (28 days)	Non-cured sealant, control: NaCl	Direct contact with non-polymerized product	4×0.03 mL	*Systemic toxicity:* no mortality, no signs of toxicity, no difference in body weight evolution, no toxicologically relevant effect, no organ weight differences, no macroscopic finding
	Subacute toxicity study with polymerized product (28 days)	Cured disk of sealant; control: HDPE disk	Direct contact with polymerized product	4 disks (40 mg)	*Local tolerance:* tissue envelope around each implant, no macroscopic findings, no test-related histopathologic findings; foreign body-type reaction of the tissue at low grade
	Subchronic toxicity study with polymerized product (13 weeks)				*Conclusion:* no evidence of systemic toxicity, test article graded as non-irritant with a dose equivalent to 40 times the maximal implanted human dose
	Chronic toxicity study with polymerized product (26 weeks)				

via orotracheal intubation). Following dissection of the carotid and heparin injection (2 mg/kg IV), one artery (alternating left or right) was clamped and partially resected. A 7-mm ePTFE graft prosthesis (Gore-Tex®, W.L. Gore and Associates, Flagstaff, AZ, USA), approximately 2 cm in length, was sutured end-to-end using Prolene (Ethicon, Somerville, NJ, USA) 5-0 to the arterial stumps. The sealant was applied on the distal or proximal anastomoses, which were selected at random, and polymerized in-situ using the proprietary LED light (30 s/cm², *i.e.* 30 s on each side of the suture line) (Figure 2). Following clamp release, the hemostasis was evaluated at both the treated and untreated anastomoses, with the latter serving as an internal control. Hemostasis was deemed as immediate or not. After the initial evaluation, the artery was reclamped and the sealant was applied to the untreated suture line. To evaluate the local tolerance of the sealant alone, the sealant was applied on the unresected untreated carotid segment. At completion of the surgical procedure, the muscular, subcutaneous and cutaneous layers were closed. Finadyne (flunixin, MSD Animal Health, Wellington, New

Figure 2.—*In-situ* polymerization (carotid/ePTFE graft suture line in sheep) of the sealant using a custom LED light source (purple color in the online version).

Zealand) 1 mg/kg IM and morphine sulphate (0.3 mg/kg/ IM twice every 24 hours) were administered at anesthesia weaning and as needed for analgesia for the first 48 hours

Table II.—*Follow-up summary:* in-vivo *preclinical studies.*

Study	N. of animal per follow-up timepoint					
	14 days	30 days	90 days	180 days	270 days	365 days
Carotid study 1 (N.=10)	N.=10	N.=10	N.=10 Sacrifice of 5 animals	N.=5 Sacrifice of last 5 animals	NA	NA
Carotid study 2 (N.=15)	N.=15	N.=15 Sacrifice of 3 animals	N.=12	N.=12 Sacrifice of 4 animals	N=8	N.=8 Sacrifice of 2 animals leaving 6 animals still alive
Aorta study (N.=8)	N.=8	N.=8 Sacrifice of 4 animals	N.=4 Sacrifice of last 4 animals	NA	NA	NA

NA: not available.

post-surgery. The ten implanted animals were evaluated at baseline, and at 14, 30, and 90 days after surgery. Five of the animals were sacrificed at 90 days. The last five animals were examined at 180 days and then sacrificed for *ex-vivo* analyses.

In carotid study 2, 15 female sheep with a mean weight of 57 kg (range: 52-64 kg) were used. All the animals underwent the same procedure from premedication to post-surgery as in carotid study 1 outlined above. This second study was designed for long-term evaluation and so the fifteen implanted animals were evaluated at baseline, at 14, 30, 90, 180, 270, and 365 days after surgery. Three animals were sacrificed at 30 days, four at 180 days, two at 365 days for *ex-vivo* analyses while six are maintained alive to date (Table II).

Aorta study

Eight female sheep with a mean weight of 60 kg (range: 50-67 kg) were used in this study. Following induction and maintenance of analgesia and anesthesia, a lateral thoracotomy was performed, and the descending thoracic aorta was dissected distal to the aortic arch. Following heparin injection (2 mg/kg), the femoral artery and the right atrium were cannulated to perform cardiopulmonary bypass (CPB). The thoracic aorta was then clamped and partially resected. An approximately 2-cm-long segment of a polyester Dacron® graft prosthesis (MAQUET®, Rastatt, Germany; 16, 18, 20, and 22 mm of diameter) was sutured end-to-end using Prolene 5-0 to the proximal and distal aortic segments. The sealant was randomly applied to either the distal or proximal anastomoses and polymerized *in situ* using the proprietary SETALIUM™ Light Pen (30 s/cm², *i.e.* 30 s on each side of the suture line). Following clamp release, the hemostasis was evaluated at both the

treated and untreated anastomoses, with the latter serving as an internal control. As before, hemostasis was classified as immediate or not. After the initial evaluation, the artery was reclamped and the sealant was applied to the untreated suture line. To evaluate the local tolerance of the sealant alone, the sealant was spread on the unresected native descending aorta. At completion of the surgical procedure, the ribs, the muscular, subcutaneous and cutaneous layers were closed. Bupivacaine 100 mg was locally injected on three sites. Finadyne (1 mg/kg IM) and morphine sulphate (0.3 mg/kg/IM twice every 24 hours) were administered at anesthesia weaning and as needed, for the first 48 hours after surgery.

The eight implanted animals were evaluated at baseline, 14, and 30 days following surgery. Half of the animals (N.=4) were sacrificed at 30 days. The last four animals were examined at 90 days and then sacrificed for *ex-vivo* analyses (Table II).

In-vivo performance evaluation criteria

Hemostasis was evaluated on the treated and non-treated anastomoses after clamp release. Clinically significant hemostasis was defined as an anastomosis not requiring any additional intervention to control bleeding from pressurization of the vessel after completion of the anastomosis until closure of the surgical wound. The anastomoses were intentionally sutured every 2 mm by the vascular surgeon to facilitate bleeding and test the sealant performance in a challenging situation. After unclamping, the occurrence of bleeding was recorded as well as its severity (no bleeding, oozing, abundant bleeding) as judged by the principal investigator.

General clinical signs (general behavior, hematology and clinical chemistry analyses) and adverse events were

monitored from the day of surgery until completion of the study. A hemodynamic evaluation was performed using ultrasound to assess the patency and the morphology of the prosthetic conduit and native vessel, and the local reaction following surgery.

EX-VIVO EVALUATION CRITERIA

Following sacrifice of the animal by lethal dose of Dolethal™ IV (Vetoquinol, Towcester, UK), a gross necropsy was performed. Target organs (brain, heart, lungs, liver, kidneys, lymph node) were examined for abnormalities and explanted for histopathology. The implants (graft and native tissue) were removed. The nature and extent of tissue reactions were observed, such as hematoma, edema, encapsulation and additional gross findings were assessed and recorded. A histopathological evaluation of the prosthetic conduit and native tissue with the sealant was performed to evaluate the local tolerance and the bioresorption over time.

First-in-human clinical study

A prospective single-arm multicenter study was designed to assess the safety and the performance of the PGSA-based SVS as an adjunct to suture in vascular reconstructions. The study was conducted in four French sites and involved six board certified vascular surgeons (ClinicalTrials.gov Identifier: NCT03374735). The study conduct was in accordance with the ethical principles of the Declaration of Helsinki, in compliance with the approved Clinical Investigation Plan (CIP), guidelines for good clinical practice (NF EN ISO 14155) and the rules governing medical devices and local regulations. Ethics Committee approval and Competent Authority authorization were obtained before study initiation, and all patients gave their written informed consent before any trial-related procedure.

Adult patients undergoing a carotid endarterectomy using an ePTFE patch were enrolled between March and September 2016. Exclusion criteria were known or suspected hypersensitivity to components of a PGSA-based sealant, intake of immunosuppressive medications, prior radiation therapy to the operating field, previous surgical procedure performed on the same operating field, current or recent (<3 months) participation in another investigational study, refusal to receive blood products, and pregnant or breast-feeding women.

Each patient participated in one assessment period and selection visit was conducted within 21 days of the carotid reconstruction. Demographic data, medical and surgi-cal history, concomitant treatments, and medical imaging showing the percentage of carotid stenosis were collected. Baseline safety assessments were performed (ECG, vital signs, and blood tests). Then, patients underwent standardized carotid endarterectomy surgery with longitudinal arteriotomy, endarterectomy, and patch angioplasty using an ePTFE Cardiovascular Patch (Acuseal, W. L. Gore & Associates) and a 6-0 polypropylene suture with a 11-mm needle. Following completion of the patch angioplasty with the artery still clamped, the PGSA-based sealant was prophylactically applied in a thin layer all along the suture line and photo-activated using the proprietary SETALIUM™ Light Pen. When blood flow was restored, the treated suture line was monitored by the operating investigator and the time to hemostasis was recorded by a trained operating room nurse using a calibrated stopwatch to assess the primary endpoint. Anesthesia (locoregional or general) was performed following the study site standard practice and the use of perioperative, intraoperative, and postoperative anticoagulation protocols was at the investigator's discretion.

Within the week following the carotid reconstruction, a postoperative visit was performed, and patients were discharged from the clinical unit at the investigator's discretion. Patients returned to the hospital for four ambulatory visits: at 1, 3, 6, and 12 months after the surgical procedure. At each visit, safety assessments were performed, including ECG, vital signs, blood tests and imaging (MRI, Doppler, CT angiography).

A Data Safety and Monitoring Committee composed of three independent medical monitors reviewed and evaluated all safety events and assessed, at given intervals, the progress of the clinical investigation, the safety data and the critical performance endpoints to advise the sponsor whether to continue, suspend, modify, or stop the clinical investigation.

The primary performance endpoint was the elapsed time from clamp release corresponding to the necessary time for the investigator to ensure and evaluate the hemostasis even if the hemostasis was instantly reached. Anastomotic hemostasis was defined as an anastomosis not requiring any additional intervention to control bleeding.

The primary safety endpoint was defined as all adverse events (related and non-related) occurring from the surgical procedure to the end of the 3-month follow-up period. The secondary performance endpoints included the elapsed time from product application to hemostasis, the proportion of patients achieving hemostasis at 0, 1, 3, 5, 10 or more minutes after clamp release; the frequency of the

use of additional adjunctive measures, and the surgery duration. Secondary safety endpoints included assessment of vital signs, ECG, imaging and blood tests throughout the study, all adverse events after 3 months up until the end of the study (one-year follow-up), and all device deficiencies were recorded during the surgical procedure.

Statistical analysis

The pre-clinical studies data were analyzed by descriptive statistics. The results are shown as the mean and standard deviation. For the *ex-vivo* local tolerance, differences in medians between the sealant and the graft materials were assessed at each measurement interval using the Mann-Whitney non-parametric U-test due to the small sample size. Significance was set at $P<0.05$. For the clinical study, a Bayesian sequential design was used to justify the appropriate sample size and to answer the primary performance endpoint, based on available data from previous clinical investigations performed with other synthetic marketed sealants.[17-19]

The study design involved a total of 34 patients split in three sequential steps and two interim analyses were planned to decide possible earlier termination of recruitment for performance or futility at 22 patients and at 28 patients. The primary goal of the study was evaluation of the superiority for the primary performance endpoint in comparison with historical literature data. The decision criterion for possible earlier termination of recruitment was based on an intention-to-treat (ITT) analysis, *i.e.* all enrolled patients except those who did not receive at least one application of the PGSA-based sealant for all reasons not related to sealant performance. If relevant, results were presented for the per protocol population, *i.e.* patients from the ITT population without any major deviation from the CIP.

To address the primary performance endpoint, a relationship was established between elapsed time from clamp release to hemostasis and the proportion of patients reaching immediate hemostasis.

The decision rule for futility or performance at each stage of the study was driven by the quantity:

$$\text{Prob} [\text{Beta}(0.5 + s, 0.5+n–s) > 0.5]$$

denoting the posterior probability of the immediate hemostasis rate, with n as the number of patients with the PGSA-based sealant application and s as the number of patients with immediate hemostasis. Performance was established if this probability was large enough. The threshold of 0.981 was chosen to maintain the overall type I error rate at 5%. Thus, performance was established if Prob≥0.981. The

Beta distribution allowed deriving the rule of decision for each stage of the study with S_{high} the minimum number (included) of immediate hemostasis above which the study is stopped for performance (Prob>0.981), and S_{low} defining the maximum number (included) of immediate hemostasis under which the study is stopped for futility (Prob<0.981 even if immediate hemostasis is observed in all subsequent patients). No statistical hypotheses were defined for the primary safety endpoint and the secondary endpoints. Results were presented with descriptive statistics.

Results

In-vivo preclinical studies

Biocompatibility assessment

The biocompatibility testing showed that the PGSA-based SVS is non-pyrogenic, non-sensitizing, non-irritant, non-clastogenic, and non-mutagenic. In addition, no acute toxicity, hemolysis, activation of the intrinsic coagulation pathway and of the human complement was observed (Table I). At a clinical equivalent dose, no cytotoxicity and no modification of cell density and cell morphology was observed as result of cell death. At 40 times the equivalent clinical dose following subcutaneous implantation, no sign of systemic toxicity was observed at 1, 3, and 6 months; the local tolerance was judged equally good and the product was not considered as irritant.

In-vivo *performance evaluation*

In carotid study 1, the hemostasis was considered clinically satisfactory for the ten anastomoses treated with the sealant, *i.e.* a 100% performance rate with non-clinically relevant bleeding and slight oozing reported in four out of the ten anastomoses. In the control anastomoses without application of the sealant, bleeding was abundant (more than 25% of needle holes bleeding) requiring additional hemostatic treatment in all cases. Following the sealant application on the ten control cases that were bleeding after the assessment, the hemostasis was fully achieved and judged clinically satisfactory in all ten anastomoses.

In carotid study 2, the hemostasis was judged by the principal investigator as clinically satisfactory for the 15 anastomoses treated with the sealant, *i.e.* a 100% performance rate, with no bleeding observed in eight anastomoses. In the control anastomoses without application of the sealant, bleeding was abundant (more than 25% of needle holes bleeding) requiring additional hemostatic treatment

in all cases. Following the sealant application on the 15 control cases that were bleeding after the assessment, the hemostasis was fully achieved and judged clinically satisfactory in all cases.

In the aorta study, the hemostasis was judged clinically satisfactory for the eight anastomoses treated with the sealant, *i.e.* a 100% performance rate with bleeding and slight oozing reported in two out of the eight anastomoses. In the control anastomoses, without application of the sealant, the bleeding was abundant (more than 25% of needle holes bleeding) requiring an additional hemostatic treatment in all cases. Following the sealant application on the 8 control cases that were bleeding after the assessment, the hemostasis was fully achieved and judged as clinically satisfactory in all eight anastomoses.

HEMODYNAMIC EVALUATION

During the follow-up period (up to 365 days) all carotid and aortic prostheses and all native vessels treated with the sealant remained fully patent in all animals.

SAFETY EVALUATION

The blood tests (biochemistry and blood cell count analyses) on all animals (N.=33) did not show any implant-related abnormalities.

Ex-vivo *evaluation*

MACROSCOPIC OBSERVATION AT NECROPSY

The full macroscopic evaluation performed during necropsy of the sacrificed animals (N.=27) at the sites of implantation (on vascular prostheses and on native tissue) and the target organs did not show any implant-related abnormality. No implant-related mineralization was recorded on X-ray evaluation.

LOCAL TOLERANCE AND BIORESORPTION

The histopathological findings at 30, 90, 180, and 365 days post-surgery of grafted and native arteries indicated an overall excellent local tolerance of the sealant, with a local reaction lower than that induced by the graft material alone (Figure 3) and a decreasing reaction over time (Figure 4). Based on the weighted average of the median values of the morphometric measurements observed across the three different studies, 43%, 64%, and 86% of the sealant was resorbed at 90, 180, and 360 days after surgery respectively compared to 30 days as baseline (no measures performed at D0) (Table III).
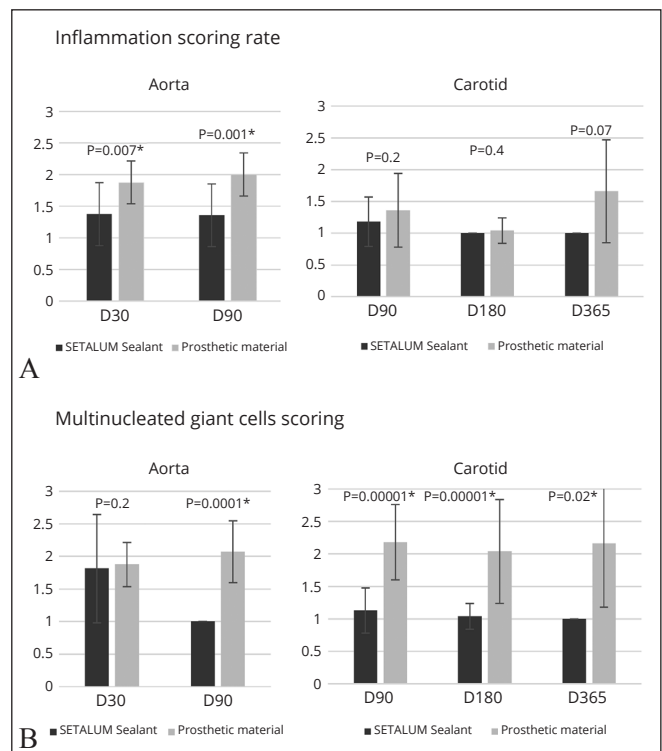

Figure 3.—Related local reaction scoring (mean±SD) following implantation of the sealant and prosthetic graft material in aorta (prosthetic material: Dacron; N.=8) or carotid artery (prosthetic material: ePTFE; N.=10) of sheep; Histopathologic generic grades were assigned as level 1 (minimal), 2 (mild), 3 (moderate), or 4 (severe) based on an increasing extent and/or complexity of change. A) Global evaluated inflammation scoring; B) scoring of multinucleated giant cells in reaction to foreign implanted body.
*Significantly less multinucleated giant cells with the PGSA than the prosthetic material (Dacron) at D90 in aorta (16 and 14 slides per group at D30 and D90 respectively) and at all time points with PGSA than prosthetic material (ePTFE) in carotid; (22, 23 and 6 slides per group at D90, D180 and D365 respectively).
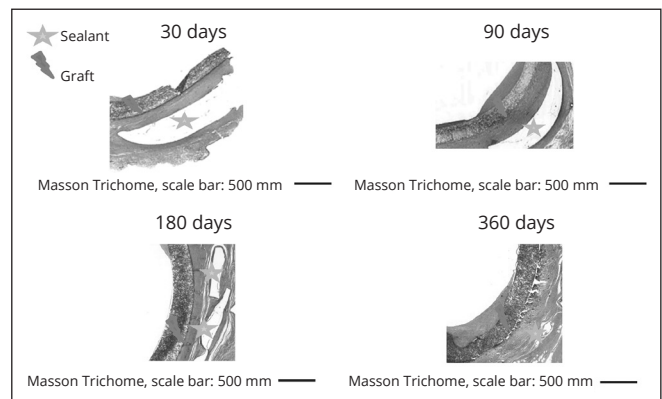

Figure 4.—Cross-section of carotid artery after implantation of the ePT-FE graft prosthesis and the sealant at 30, 90, 180, and 360 days after implantation showing gradual resorption of the sealant.

TABLE III.—*Morphomeric measurements of the bioresorption of the PGSA-based sealant.*

Measurements	30 days	90 days	180 days	360 days
Absolute area of the grafted arteries, mm^2 *	5.3±2.0*	3.0±0.8*	1.9±0.4*	0.8±NA*
Percentage of remaining absolute area of the grafted arteries**	100±38	57±15	36±8	14±NA*
Percentage of resorption	0	43	64	86

NA: not available.
*Weighted average and associated standard deviations of the median values observed 1, 3, 6 days and 12 months post-implantation in the three animal studies; **first time point (*i.e.* 1 month) was defined as 100% of implanted Sealant as worst case, since the initial implanted surface cannot be determined.

TABLE IV.—*Decision criteria for futility and performance at each stage of the clinical study.*

Stage	S_{low}	S_{high}
Stage 1 (N.=22 patients)	10	16
Stage 2 (N.=28 patients)	16	20
Stage 3 (N.=34 patients)	22	23

Clinical study

Seventeen instances of immediate hemostasis were observed at Stage 1. Therefore, the recruitment was stopped at the sample size of 22 patients (ITT population) per the futility and performance decision criteria (Table IV). The per protocol-(PP) population comprised 19 patients. All patients completed the one-year follow-up period.

The study population was predominantly male (59.1%). The mean age at surgery was 69 years and the mean BMI 24.8 kg/m^2. All the patients presented with severe carotid stenosis (at least 70% stenosis), of which 95.5% were asymptomatic (Table V).

Out of the 22 enrolled patients, the median elapsed time from clamp release to hemostasis could be assessed for 21 patients and the result was 11 s (IQR: 00:09-00:57) (Table VI).

With 17 instances of immediate hemostasis as defined in the primary performance endpoint and five patients necessitating additional adjunctive measures to achieve hemostasis, the primary performance criterion was fulfilled with a performance rate of 77.3% in the ITT population and 84.2% in the PP population (16 immediate hemostasis). Among the 17 patients reaching immediate hemostasis, the median elapsed time from clamp release to hemostasis was 10 s (IQR: 00:09-00:22). For one patient, the elapsed time from clamp release to hemostasis was four minutes, but no additional adjunctive measure was used. According to the operating investigator, due to the injury of a small collateral artery located near the patch, two stitches were added on a neighboring glomus artery that was bleeding at clamp release. Five patients (22.7%) needed additional adjunctive measures to achieve hemostasis: *i.e.*, re-use of PGSA-based sealant, addition of stiches, or Surgicel®

TABLE V.—*Baseline characteristics of the clinical study patients.*

Parameters	ITT population (N.=22)
Age, years	69.0±10.6
Gender	
Female	9 (40.9%)
Male	13 (59.1%)
BMI, kg/m^2	24.8±4.8
Carotid endarterectomy	
Stenosis ≥70% (severe)	22 (100%)
Symptomatic	1 (4.5%)
Asymptomatic	21 (95.5%)
Medical history (main classes)	
Diseases of the circulatory system	49 (29.2%)
Endocrine, nutritional and metabolic diseases	33 (19.6%)
Concomitant treatment (main class)	
Patients with at least one anticoagulant/antiplatelet agent	20 (90.9%)
Patients with at least one curative anticoagulant agent	2 (9.1%)
Tinzaparin	1
Sodium heparin	1
Patients with at least one antiplatelet agent	18 (81.8%)
Clopidogrel	4 (18.2%)
Lysine acetylsalicylate	14 (63.6%)
Patient with at least dual antiplatelet therapy	1 (4.5%)
Clopidogrel + lysine acetylsalicylate	1 (4.5%)

Data presented as mean±SD or as number of cases (proportion).
ITT: intention-to-treat.

(Johnson & Johnson, New Brunswick, NJ, USA) application (Table VI).

In terms of secondary performance endpoints, the median elapsed time from product application to hemostasis (including vessel clamping and unclamping) was 3:30 (IQR: 02:49-05:30) and thus, the product application steps (*i.e.*, application and photo-activation of the sealant) took approximately three minutes. 72.7% of patients (16 of 22) achieved hemostasis within the first minute following application and the mean duration of the carotid endarterectomy was 49:05 (±13.0) with a median at 47:02 (Table VII). Of the five patients who achieved hemostasis in over 10 minutes, three required one additional stich and two required two additional stiches.

Within the one-year follow-up period, 33 adverse events (AEs) occurred in 16 of the 22 enrolled patients (Table

TABLE VI.—*Surgical aspects and primary endpoint parameters in the clinical study.*

Parameters	ITT population (N.=22)		All patients (N.=22)
	Immediate hemostasis (N.=17)	Non-immediate hemostasis (N.=5)	
Type of anesthesia			
Local	11 (64.7%)	1 (20.0%)	12 (54.5%)
General	6 (35.3%)	4 (80.0%)	10 (45.5%)
ePTFE patch			
Width, mm	8.2±1.9	8.4±1.5	8.2±1.8
Length, cm	4.0±0.8	3.5±1.0	3.9±0.9
Quantity of sealant used per surgery, mL	0.3±0.1	0.2±0.0	0.3±0.1
Protamine use	10 (58.8%)	2 (40.0%)	12 (54.4%)
Elapsed time from clamp release to hemostasis, min:s			
Mean±SD	00:29±00:57	07:08±03:07	01:45±03:03
Median	00:10	07:58	00:11
Range	00:01-04:00*	02:46-9:50	00:01-9:50
1st-3rd quartile	00:09-00:22	06:00-09:05	00:09-00:57
Patients requiring additional measures	0 (0%)	5 (100%)	5 (100%)

Data presented as mean±SD or as number of cases (proportion).
ITT: intention-to-treat.
*For one patient, the time to hemostasis was 4 min and was classified in the sub-group of immediate hemostasis.

TABLE VII.—*Secondary performance results of the clinical study.*

Parameters	ITT population (N.=22)
Elapsed time from product application to hemostasis, min:s	
Mean±SD	04:50±03:17
Median	03:33
Range	01:58-13:12
Proportion of patients reaching hemostasis at:	
0 to under 1 min	16 (72.7%)
1 to under 3 min	0 (0%)
3 to under 5 min	1 (4.6%)
5 to under 10 min	0 (0%)
≥10 min*	5 (22.7%)
Surgery duration, min	
Mean±SD	49.5±13.0
Median	47.2
Range	35.4±100
Additional adjunctive measures	
Re-use of PGSA-based sealant	2 (22.2%)
Surgicel® application	2 (22.2%)
Stitch addition	5 (55.6%)

ITT: intention-to-treat.
*Censored observations: when additional adjunctive measures were used to achieve hemostasis, those patients were classified in the ≥10 min group.

TABLE VIII.—*Adverse events (AEs) and severe adverse events (SAEs) reported in the clinical study (safety population, N.=22).*

Adverse events	AEs (N.=26)	SAEs (N.=7)
Surgery to 3 months (primary endpoint)		
Tachyarrhythmia due to an atrial fibrillation	–	1
Left iliopsoas muscle hematoma	–	1
Pneumonia	–	1
Other	20	–
3 months to 1 year (secondary endpoint)		
General physical deterioration	–	2
High grade atrioventricular block	–	1
Cardiac decompensation	–	1
Other	6	–

VIII). Seven AEs were considered serious and unrelated to the PGSA-based SVS, accessories, and its application method according to both the investigators and the independent Safety Data Monitoring Committee. No death occurred during the study. 26 AEs were classified as nonserious and were not considered by the investigators as being related to the PGSA-based sealant and accessories. Among them, ten AEs such as anemia (N.=1), hematoma (N.=1), and transient left inferior laryngeal nerve palsy (N.=1), were considered related to the carotid endarterectomy and 14 AEs were considered related to the patients' medical history.

Additional safety assessments by ECG, vital signs, blood tests and imaging did not reveal any abnormal change over the course of the study.

Discussion

Bleeding at the anastomotic suture line is a significant clinical issue that can lead to an increase in surgical procedure time and postoperative complications.[20] To help surgeons solve this issue, several local hemostatic products have been developed and more specifically vascular sealants. To ensure the best safety and efficacy, an ideal

adjunct-to-suture sealant should be safe and biocompatible, fully synthetic to mitigate an immune response, bioresorbable following the complete vascular tissue healing process, exhibit an optimal adhesion to vascular tissue, remain elastic and adaptable to mechanical deformation, usable in a wet environment with minimal washout, and have on-demand activation to enable a controlled and safe application. The new PGSA-based SVS, as demonstrated in the current studies, satisfies all the above requirements.

Previous studies have demonstrated its capacity to be applied onto tissue even following blood exposure due to its hydrophobicity and high viscosity that maximizes intimate tissue contact and minimizes washout.[13] Its on-demand light-activated polymerization allows the user full control over its application: the sealant can be applied without a time constraint as it polymerizes only once the proprietary LED light is used for activation. When needed, a fast light activation (30 s/cm^{2}) polymerizes the sealant, provides hemostasis, and allows unclamping of vascular conduits without further delay. Furthermore, the new PGSA-based sealant has been designed to comply with tissue deformation following in-situ polymerization.[14]

Its biocompatibility results at an equivalent clinical dose and up to 40 times the equivalent intended clinical dose, were excellent. Moreover, following implantation of the PGSA-based sealant in clinically relevant animal models, no toxic effect, no related clinical signs, and no macroscopic and histological abnormalities occurred at all implantation time points tested. With the thin sealant layers applied and the absence of swelling of the sealant, no compression of surrounding organs has been observed throughout the follow-up period. The local tolerance of the PGSA-based sealant material was judged excellent by the histopathologist with minimal local inflammation and foreign body reaction following implantation of the sealant; the reaction was found to be lower than the reactions obtained with ePTFE and Dacron materials alone. Below the implanted sealant, a complete and unobstructed healing process of the vascular tissue was observed, with a normal endothelialization of the graft material, without abnormalities or sealant-related calcification. Moreover, even the minimal reactions observed decreased over time. As the sealant product is fully synthetic, no specific immunological effects or viral infection were observed.

The present study shows an excellent performance of the PGSA-based SVS in three vascular surgery animal studies, with good adhesion regardless of the substrate. The adhesion is obtained by a mechanical process: it has been demonstrated that the pre-polymer infiltrates into the upper layer of the substrate and following its polymerization, its interlocking with fibers of the substrate ensures its good adhesion. Indeed, following its fast polymerization (30 s/cm^{2}), the sealant forms a hermetic blood-proof barrier and provides an immediate hemostasis after clamp release (100% success in all the animals). Thanks to its high viscosity and hydrophobicity, the product does not wash away with biological fluids during use and is easy to spread as a thin layer onto the suture line. Moreover, no product-related stenosis or hemodynamic changes have been induced following implantation and throughout the follow-up periods. The sealant therefore exhibits a high degree of performance.

The bioresorption of the sealant, based on a surface erosion mechanism by hydrolysis and enzymatic esterase reactions,[14] is gradual up to 86% at 12 months as shown in animal models, with a full resorption expected within 18-24 months. In comparison, some current available sealants degrade very fast, potentially before completion of the vascular tissue healing process. Indeed, the normal fibrinolysis degrades the fibrin clot in one to two weeks and the PEG sealants are fully biodegraded by phagocytosis within a maximum of 30 days.[6] On the other hand, some sealants such as acrylic compounds degrade very slowly (25% within 24 months), inducing risks related to long-term inflammation processes such as hypersensitivity.[9, 10]

For the first in-human use of the PGSA-based SVS, a standardized model of peripheral vascular surgery using ePTFE graft, one of the most hemorrhagic grafts, was chosen. Carotid endarterectomy is a highly reproducible surgery and carotid repair using patch angioplasty is the standard technique in all centers involved in the study. Baseline characteristics of this study population were representative of patients requiring carotid endarterectomy (elderly patients with a slight majority of men, suffering from severe stenosis with several risk factors).[21, 22]

Time to secure an effective hemostasis is a commonly used criterion in clinical studies to evaluate surgical sealants. For the PGSA-based sealant, the median elapsed time from clamp release to hemostasis was 11 s. About 77.3% of the patients had an immediate hemostasis in the ITT population and 84.2% in the PP population. These results are comparable to other studies evaluating surgical sealants (Table IX).

Moreover, the surgery duration was not substantially extended by the application and photo-activation of the PGSA-based sealant which took approximately 3 min.=The mean elapsed time from product application to hemostasis of 04:50 compared favorably with oxidized regenerated

TABLE IX.—*Comparison between PGSA-based sealant and other sealants.*[7, 17, 19, 23-25]

Study	Product	N. of cases	Mean elapsed time from clamp release to hemostasis	Immediate hemostasis	Procedure/comments
Present study	SETALIUM™ Vascular Sealant (TISSIUM)	22	1 min 45 s	ITT: 77.3% PP: 84.2%	Vascular reconstruction using an ePTFE patch
Schenk *et al.*[17]	Omnex® (Ethicon)	151	1 min 59 s	54.3%	Bypass graft AV access graft
Duarte *et al.*[7]	Omnex® (Ethicon)	105	23.2 s	71.3%	AV access vascular reconstruction
Schenk *et al.*[19]	ArterX® (Baxter)	217	5.1 min	60.5%	Vascular graft or patch, AV access, Arteriotomy
Florek *et al.*[23]	Coseal® (Baxter Healthcare Corp)	148	16.5 s	47%	AV shunt dialysis access
Glickman *et al.*[24]	Bioglue® (Cryolife)	151	NA	60.5%	Bypass graft Cardiac procedures
Coselli *et al.*[25]	Bioglue® (Cryolife)	40	11 min	NA	Carotid endarterectomy with ePTFE graft

NA: not available; ITT: intention-to-treat; PP: per protocol.

cellulose (13:06), fibrin sealant (03:36) and pressure application (21:09).[17]

Based on literature data of other synthetic marketed sealants,[4, 8, 18-20, 23-27] potential AEs related to product application could be: failure of the sealant to adhere to the tissue, a hypersensitivity reaction, a local or systemic effect, an application of the sealant to tissue not targeted for the surgical procedure, thrombosis and thromboembolism. Following the PGSA-based sealant application, none of these events were observed through the one-year safety follow-up period. In addition, no AE was considered related to the sealant and accessories, nor its application method. No serious adverse event (SAE) linked to the surgical procedure such as death, stroke, myocardial infraction, cranial nerve injury and hematoma necessitating reoperation occurred. Some expected non-serious AEs (ten AEs, *i.e.*: 30.3% of total AEs) following carotid endarterectomy were reported: inflammation, anemia, hematoma and transient damage of left vagus nerve. The reported safety data in this study are representative of those occurring in patients requiring vascular reconstructions (*i.e.*: elderly patients with multiple risk factors). Indeed, 14 AEs, including five SAEs (42.4% of all AEs), were considered as being related to the medical history.

Limitations of the study

The limitation of the preliminary clinical investigation was the single arm open-label design with a small sample size. However, the sample size calculation was based on a robust Bayesian model allowing to determine the required patients' sample for the study primary endpoint assessment. In addition, care was given to the minimization of intraoperative bias for the primary performance endpoint evaluation by standardizing the assessment of time to hemostasis across investigational sites and clearly defining notions of "hemostasis" and "immediate hemostasis." Additional potential bias was reduced by appointing independent personnel who source-verified and analyzed the data and by establishing an independent Safety Data Monitoring Committee to assess the performance and safety data throughout the study.

Conclusions

The new PGSA-based SVS exhibits an optimal in-vivo performance and bioresorption as an adjunct to sutures in vascular surgery in animal (ovine) models. Pre-clinical data showed an excellent local tolerance of the product, with no related adverse events and good healing features. The good safety and performance profile of the new PGSA sealant was confirmed in the first clinical investigation with a favorable clinical outcome in patients requiring hemostasis along carotid suture lines and without any undue safety concerns. Any risks associated with the use of the device was acceptable when weighed against the benefits to the patient. These promising first-in-human results of the new CE-marked PGSA-based sealant serve as an important foundation to advance a new generation of biodegradable elastic adhesive materials into clinical practice.

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