DE NOVO CLASSIFICATION REQUEST FOR ALLAY NERVE CAP

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **In situ polymerizing peripheral nerve cap**. An in situ polymerizing peripheral nerve cap is a prescription use only device composed of precursor materials that polymerize when delivered to the end of a peripheral nerve to function as a physical barrier to the surrounding in vivo environment to reduce the risk of formation of a symptomatic neuroma.

NEW REGULATION NUMBER: 21 CFR 882.5260

CLASSIFICATION: Class II

PRODUCT CODE: SBG

BACKGROUND

DEVICE NAME: allay Nerve Cap

SUBMISSION NUMBER: DEN230061

DATE DE NOVO RECEIVED: September 19, 2023

CONTACT: Tulavi Therapeutics
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INDICATIONS FOR USE

The allay Nerve Cap is indicated for use in adults aged 22 years or older as a physical barrier to separate the peripheral nerve end from the surrounding environment to reduce the risk of the development of a symptomatic neuroma.

LIMITATIONS

The allay Nerve Cap is not designed, sold, or intended for use except as described in the indications for use and is contraindicated for use in:

- Areas of active surgical site infection.
- Areas of active blood flow.
- Areas of excessive movement or over a joint.

- Patients with a known allergy to poly(ethylene glycol) (PEG) or the color additives FD&C Yellow No. 5 Dye (tartrazine) or FD&C Blue No. 1 Dye (brilliant blue FCF).

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS

DEVICE DESCRIPTION

The allay Nerve Cap is a sterile, absorbable, in situ formed, hydrogel composed of water and polyethylene glycol (PEG). The hydrogel forms in seconds after delivery of the precursor solutions around a nerve seated in a temporary silicone Cap Form (Figure 1). The hydrogel provides a transparent, compliant nerve cover that conforms to and provides non-constricting encasement of the nerve. The Cap Form is removed and discarded after the implantation procedure. The hydrogel nerve cap is absorbed within 8 months.

The allay Nerve Cap system is provided in a plastic tray sealed in a sterile, peelable outer pouch. The product is available in two sizes of a Small Nerve Set, for nerves less than 4 mm in diameter, and a Large Nerve Set, for nerves greater than 4 mm in diameter and less than 7 mm in diameter. The allay Nerve Cap system includes a Powder Vial/Vial Adapter, Diluent Solution, Acceleration Solution, Dual Applicator and Adapter, Delivery Tip with Blunt Needle, and the Cap Forms [Small Nerve Set (1, 2, 3, and 4 mm) and Large Nerve Set (5, 6, and 7 mm)].

Figure 1: Prepared hydrogel precursors ready for delivery in delivery system (applicator) with available cap form sizes.

The delivery mechanism of the starting materials to the site of application, the polymerization mechanism and polymer structure, the intermediate and side products produced, and degradation pathway and degradants were described in the device description of the allay Nerve Cap. The characterization of the polymerization reaction to form PEG-based hydrogels was supported by the published scientific literature.[1,2,3,4,5,6] Additionally, the material safety data sheets (MSDS), certificates of analysis, and incoming inspection results were provided for the device raw and precursor materials.

SUMMARY OF NONCLINICAL/BENCH STUDIES

[1] Reid, et al. 2015. "PEG Hydrogel Degradation and the Role of the Surrounding Tissue Environment." J Tissue Eng Regen Med, 9(3), 315-318.
[2] Fruijtier-Polloth (2005). "Safety assessment of polyethylene glycols (PEGs) and their derivatives as used in cosmetic products." Toxicology 214: 1-38.
[3] Yamaoka, et al. (1994). "Distribution and tissue uptake of poly (ethylene glycol) with different molecular weights after intravenous administration in mice." J. Pharm. Sc. 83: 601.
[4] Sharda, N. et al. (2021) "Pharmacokinetics of 40 kDa polyethylene glycol (PEG) in mice, rats, cynomolgus monkeys and predicted pharmacokinetics in humans." European Journal of Pharmaceutical Sciences. 165, 105928.

BIOCOMPATIBILITY/MATERIALS

The allay Nerve Cap is a long-term contact implant (> 30 days) in contact with tissue/bone. As such, its biocompatibility evaluation was conducted in accordance with ISO 10993-1:2018, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process," and the FDA guidance, "Use of International Standard ISO-10993, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"." For a long-term contact implant in contact with tissue/bone, the allay Nerve Cap was evaluated for the following: physical and chemical information, cytotoxicity, sensitization, irritation or intracutaneous reactivity, material-mediated pyrogenicity, acute systemic toxicity, subacute/subchronic toxicity, chronic toxicity, implantation, hemocompatibility, genotoxicity, carcinogenicity, and neurotoxicity. As part of this biocompatibility evaluation, the materials of construction (direct, indirect) including the hydrogel and degradation products, the Applicator and the Cap Forms, the packaging materials including the tray, and any additives that might arise from the manufacturing process were assessed (see Table 1).

Table 1: Biocompatibility Evaluations for the allay Nerve Cap System

Test	Test Method	Results
allay Nerve Cap		
Cytotoxicity	ISO 10993-5:2009, ISO Elution Method	Non-cytotoxic
Sensitization	ISO 10993-10:2010, Maximization Test in Guinea Pigs	Non-sensitizing
Intracutaneous Irritation	ISO 10993-10:2010, Intracutaneous Reactivity in Rabbits	Non-irritant
Acute Systemic Toxicity	ISO 10993-11:2017, Acute Systemic Toxicity in Mice	Non-toxic
Implantation	ISO 10993-6:2016, Local Subcutaneous Implantation, 2 Weeks, 13 Weeks, 26 Weeks	Non-irritant
In vivo Animal Study Efficacy – Local Implantation at Clinically Relevant Site	Hydrogel Formed in situ Around Transected Nerve in Cap Form, 4 Weeks, 12 Weeks Hydrogel Formed in situ Around Sciatic Nerve, 6 Months, 8 Months	Non-irritant Non-compressive No migration or adverse tissue responses or effects observed
Neurotoxicity	ISO 10993-1 and ASTM F2901-19, 4 Weeks, 12 Weeks, 6 Months, 8 Months	Non-irritant No adverse responses were observed
Repeated Exposure Systemic Toxicity	Chemical Characterization and Toxicological Risk Assessment (TRA)	Non-toxic

[5] Webster, et al. (2007). "PEGylated Proteins: Evaluation of their safety in the absence of Definitive Metabolism Studies." Drug Metab Disposition, 35(1), 9-16.

[6] Longley, et al. (2013). "Biodistribution and excretion of radiolabeled 40 kDa polyethylene glycol following intravenous administration in mice." J Pharm Sc 10,2(7), p. 2362-2370.

Test	Test Method	Results
(Subacute, Subchronic, Chronic)		
Hemolysis (Indirect Contact)	ISO 10993-4:2017 and ASTM F756	Non-hemolytic
Pyrogenicity	ISO 10993-11:2017 and USP 34 <151>, USP Rabbit Pyrogen Study, Material Mediated	Non-pyrogenic
Genotoxicity	ISO 10993-3:2014, Bacterial Reverse Mutation Test (Ames Assay), in situ Formed	Non-genotoxic
	ISO 10993-3:2014, Bacterial Reverse Mutation Test (Ames Assay), in Cap Form	
	ISO 10993-3:2014, Bacterial Reverse Mutation Test (Ames Assay), Fully Degraded	
	ISO 10993-3:2014, Mouse Lymphoma Assay, Dose Finding, in situ Formed	
	ISO 10993-3:2014, Mouse Lymphoma Assay, Dose Finding, in Cap Form	
	ISO 10993-3:2014, Mouse Lymphoma Assay, Dose Finding, Fully Degraded	
Reproductive Toxicity	Chemical Characterization and TRA	Non-toxic
Carcinogenicity	Chemical Characterization and TRA	Non-carcinogenic
Sterile Cap Forms		
Cytotoxicity	ISO 10993-5:2009, ISO Elution Method	Non-cytotoxic
Intracutaneous Irritation	ISO 10993-10:2010, Intracutaneous Reactivity in Rabbits	Non-irritant
Acute Systemic Toxicity	ISO 10993-11:2017, Acute Systemic Toxicity in Mice	Non-toxic
Pyrogenicity	ISO 10993-11:2017 and USP 34 <151>, USP Rabbit Pyrogen Study, Material Mediated	Non-pyrogenic
Sterile Applicator		
Cytotoxicity	ISO-10993-5, ISO Elution Method	Non-cytotoxic
Sterile Tray Packaging		
Cytotoxicity	ISO-10993-5, ISO Elution Method	Non-cytotoxic
Infrared Spectroscopy	Infrared Analysis per ASTM F2475-20 and ISO 10993-18:2020	No adverse effects observed
Nonvolatile Residue	USP Physiochemical Tests for Plastic (Aqueous), Non-Volatile Residue (USP	Residue ≤ 15 mg

Test	Test Method	Results
	43, NF 38, General Chapter <661>) and ASTM F2475-20, Appendix XI	
Particulates	Particulate Analysis, Light Obscuration Method per USP 43, NF 38, General Chapter <788>	No adverse particulates observed

Chemical Characterization and Toxicological Risk Assessment (TRA):

In order to assess the risks associated with the allay Nerve Cap resulting in an adverse tissue reaction or systemic toxicity effects, chemical characterization and subsequent TRA of the hydrogel under worst-case clinical conditions was performed, including identification and quantification of all detected entities extracted from the in situ formed hydrogel, the hydrogel after formation in the Cap Form, as well as the partially and fully degraded hydrogel. The characterization of the entire final finished product ensures that any potential residual chemicals from the manufacturing, packaging, or sterilization processes that could leach from the device during clinical use are not present at levels capable of causing adverse biological responses in patients implanted with the device. The TRA concluded that the extractables from the test article, the allay Nerve Cap, are unlikely to pose a toxicological safety concern. Based on the safety of the allay Nerve Cap as assessed by chemical characterization and TRA, the systemic toxicity (subacute, subchronic, and chronic), reproductive toxicity and carcinogenicity endpoints were evaluated using this testing approach in lieu of the biological testing recommended in ISO 10993-1, annex A.

SHELF LIFE/STERILITY

The allay Nerve Cap and its packaging has been validated for a shelf life of 2 years supported by performance testing using both accelerated aged and real-time aged test samples that were subjected to preconditioning and packaging distribution conditions. The results showed the final product packaging protects the product and maintains sterility under worst-case shipping, handling, and storage conditions.

The allay Nerve Cap is provided sterile using electron beam (E-beam) sterilization and is intended for single use only. The final finished product is sterilized to a sterility assurance level (SAL) of 10^{-6} using E-beam radiation. E-beam sterilization achieves a minimum internal dose of 25 kGy using the VD_{max25} method for the allay Nerve Cap.

Bacterial endotoxin testing using the limulus amebocyte lysate (LAL) kinetic chromogenic test method was evaluated for the allay Nerve Cap to meet the endotoxin limit of ≤ 20 endotoxin units (EU)/device. Bacterial endotoxin testing will be performed on each lot of the allay Nerve Cap as part of the manufacturing process.

PERFORMANCE TESTING – BENCH

Non-clinical bench testing was performed to demonstrate that the device can function as

intended under clinical conditions of use and mitigate the risks to health (e.g., adverse tissue reaction, tissue injury, use error). The non-clinical bench testing performed are presented in Table 2. All tests met pre-defined acceptance criteria.

Table 2: Summary of Non-Clinical Bench Testing for the allay Nerve Cap

Test	Test Purpose and Description
Color Additive Exposure Contact Category	The color additive is provided in the allay Nerve Cap to permit intraoperative visualization of the hydrogel relative to the tissue and in vivo background. The dissolution of color additive from the allay Nerve Cap within 72 hours was confirmed through in vitro dissolution testing on hydrogel cylinders and in situ formed hydrogel, which leaves behind a colorless, transparent hydrogel. The extracts show no change in color or turbidity and there were no visible particulates.
Determination of pH and Osmolarity	An evaluation of the physiochemical characteristics (pH, osmolality) of the precursor device components and the in situ formed allay Nerve Cap was performed for characterization.
Hydrogel Deliverability	Performance benchtop evaluation of hydrogel injectability was conducted to demonstrate that in situ crosslinking of the allay Nerve Cap is reproducible and results in homogenous hydrogel delivered across the full range of Cap Form sizes. Study design included an assessment of hydrogel deliverability under worst-case conditions including delivery at different angles and locations of injection and after the maximal introduction of bubbles into the precursor solutions prior to delivery. Hydrogel delivery was successful across all worst-case conditions in all Cap Form sizes. In addition to the worst-case deliverability assessments, performance benchtop evaluations of the range of suitable nerve sizes for each allay Nerve Cap was performed. The study was designed to ensure that the available range of Cap Form sizes are suitable for delivery of the hydrogel around each respective nerve size. The hydrogel was successfully delivered around the range of nerve sizes per the Instructions for Use and the Cap Form was successfully removed without breaking or damaging the in situ formed allay Nerve Cap.
Dimensional Evaluation	Dimensional evaluation was conducted to assess the hydrogel physical dimensions and volume including confirming nerve encapsulation within the hydrogel for each nerve size per the Instructions for Use, measurement of gel dimensions (length, width, volume) for each Cap Form size, and assessment of the appropriate nerve sizes for each Cap Form.
Dimensional Stability	To achieve the intended use of the allay Nerve Cap, the hydrogel must maintain integrity as a protective layer around the end of the nerve without significant loss of mechanical strength for at least three months. In vitro dimensional stability testing was conducted to demonstrate the integrity and persistence of the hydrogel under real-time physiologic conditions (37 °C, phosphate buffered saline (PBS),

Test	Test Purpose and Description
	pH 7.4) for at least four months (16 weeks), including the ability of the hydrogel to maintain a protective layer around the nerve and maintain lumen patency past the three-month time frame during which neuroma formation could occur after nerve transection. As part of this evaluation, maintenance of hydrogel integrity without cracks or collapse, mechanical strength (compressive modulus), and lumen patency with no substantial dimensional loss were demonstrated. In addition, minimal swelling of the hydrogel was demonstrated. The dimensional stability of the allay Nerve Cap, as assessed by visual observation and dimensional measurements, was also demonstrated at clinically relevant but worst-case physiologic extremes of osmolarity. At an extreme range of 240 mOsm/kg to 320 mOsm/kg, there were no significant changes to the hydrogel integrity (no evidence of cracks or collapse), dimensions, or swelling (within product specifications).
Dissolution Time	The time between injection of the Diluent Solution into the Powder Vial and the complete dissolution of the powder is defined as the 'dissolution time.' This test demonstrated that the dissolution time is maintained under 5 minutes.
Gel Time	The time between the start of advancing the contents of the Applicator through the mixer and the onset of gelation is defined as the 'gel time.' The test was performed to demonstrate that the hydrogel can consistently fill the Cap Form with a gel time of less than 10 seconds to ensure there is no significant delay in the procedure.
Percent Swelling	The allay Nerve Cap is formed into cylinders (6 mm diameter, 6 mm long). The hydrogels are weighed and equilibrated in a PBS solution (pH 7.4) at 37 °C for 24 hours. After 24 hours, the cylinder is removed from the solution and weighed. This test was performed to characterize the maximal percent swelling of the hydrogel. The acceptance criteria for this test was the swelling must be between 0% and 45% swelling of the crosslinked hydrogel as measured by weight 24 hours after immersion in PBS @ 37 °C.
Compression and Rebound Testing	Transverse compression testing is performed on the hydrogel to demonstrate the hydrogel can withstand compressive forces greater than 0.25 N/cm and then rebound following removal of the force. A high threshold was established to ensure that the hydrogel rebounds > 95% ensuring good crosslinking of the polymer.
Compressive Modulus	The compressive properties of the allay Nerve Cap are measured to ensure the hydrogel has sufficient integrity to prevent nerve outgrowth in the gel and sufficient cross-linking density to persist at the site around the nerve for 8 months while remaining soft and compliant on delivery. The acceptance criteria for this test was the device must have a minimum of 30 KPa compressive modulus of the crosslinked hydrogel after 24 hours

Test	Test Purpose and Description
	in PBS.
Ease of Preparation	Ease of preparation is defined by the time it takes to assemble the allay Nerve Cap from the initial step of the hydrogel preparation to the time at which the Applicator is ready for delivery of the hydrogel. A preparation time longer than 10 minutes indicates PEG melting or that the PEG powder was stored in inappropriate conditions. The device must be able to be prepared in less than 10 minutes.
Pressure Testing	Benchtop pressure testing was conducted to demonstrate that there was no increase in pressure on an artificial nerve using a pressure transducer as a function of time after formation and equilibration of the allay Nerve Cap under physiologic conditions. The study demonstrated that no pressure was exerted on the artificial nerve at any time during hydrogel equilibration. Therefore, the allay Nerve Cap is non-compressive.
Device Migration	E*x vivo* benchtop testing was conducted on a range of freshly harvested ovine nerves to confirm that the allay Nerve Cap adheres to a clinically relevant range of nerve sizes (diameters) for up to one week under physiologic conditions to mitigate against device migration both off of the nerve and subsequently from the implant site. As the *in vivo* animal testing demonstrated no device migration on smaller nerves (1 mm rat sciatic nerve, 2 mm rabbit sciatic nerve for up to 6 months), a range of larger nerves were evaluated, at minimum establishing the ability to deliver the allay Nerve Cap around small to medium (1 to 4 mm nerves, 1 to 4 mm Cap Forms, Small Nerve Set) and up to the maximum 7 mm nerve (7 mm Cap Form, Large Nerve Set). Testing established that it was not possible to remove the allay Nerve Cap after firmly pulling on the hydrogel with forceps in an attempt to remove the hydrogel, consistent with the in vivo animal testing results demonstrating that the hydrogel maintains adherence to the transected nerve stump. Therefore, the hydrogel does not migrate off of the nerve end as established both through in vitro and in vivo animal testing.
Wear Resistance Testing	Accelerated wear testing was performed on the allay Nerve Cap to evaluate the ability of the device to resist wear. The allay Nerve Cap, delivered around an artificial nerve and placed in a clinically relevant orientation between two muscle layers (ex vivo chicken muscle), underwent (b)(4) -cm passes to evaluate any wear debris generated from the hydrogel implants under compressive, shear, and dynamic mechanical loads. The device passed the acceptance criteria that there was no mass loss and no visible particulates released from the hydrogel.
Mass Loss	An evaluation of the hydrogel mass loss over the course of accelerated degradation of the implant was performed in vitro. The mass of the allay Nerve Cap is characterized by three phases of mass loss. The study established minimal mass loss occurred over the 3-

Test	Test Purpose and Description
	month period post implantation (2.8%, 6 days). In the first phase, spanning 8 days (comparable to 4 months in vivo), only 6.6% mass loss occurs. In the second phase of mass loss, between 8 and 15 days (between 4 months and ~7.5 months), substantial degradation is occurring, over 39.8% of the mass is lost. In the third and final stage of rapid mass loss, between day 15 and 16, the remaining 44.2% of mass loss occurs.
Exaggerated Clinical Use Conditions	In addition to the in vivo assessment of delivery of the in situ forming hydrogel around the rat and rabbit sciatic nerves after transection, an ex vivo evaluation of the hydrogel performance after delivery under exaggerated clinical use conditions was performed. This represents a worst-case clinical scenario as the proposed Instructions for Use direct the surgeon not to use the device in a region of active blood flow. Hydrogel integrity was assessed after delivery directly into a Wrap Form (identical to a Cap Form but with an entrance and an exit) containing either a) fresh harvested rat blood or b) saline (mimicking physiologic fluids and/or irrigation solution). The hydrogel formed successfully in the presence of blood or saline, integrating with the blood and saline to form an intact allay Nerve Cap. No visible particulates were formed.
Use Errors	Benchtop testing was performed to evaluate whether use errors relating to hydrogel preparation and delivery that might result in poor quality hydrogel formation could impact device performance. The study was designed to evaluate the impact of each use error on device performance both immediately after hydrogel preparation and after the equivalent of 3 months degradation in vivo (6 to 8 days accelerated degradation). Hydrogels were prepared according to each worst-case use error and compared with hydrogels formed as intended per the proposed Instructions for Use. The use errors, including bubble generation, incomplete dissolution of the powder, exceeding the delivery window, or fluids did not result in significantly earlier degradation of the hydrogel, the hydrogel quality, or affect the durability of the hydrogel as measured through engineering performance testing.
Human Factors and Usability	A human factors and usability study was conducted to evaluate the design and usability of the allay Nerve Cap for the intended users, uses and use environment. The study evaluated the device in the sterile final finished form, including the final commercial packaging and tray configuration following the proposed Instructions for Use. The study design was informed by the FDA guidance, "Applying Human Factors and Usability Engineering to Medical Devices," ISO 14971:2019, "Application of risk management to medical devices," ISO 13485:2015, "Medical Devices - Quality management systems – Requirements for regulatory purposes," clause 7.3.3a, IEC 62366-1: 2015, "Medical devices - Part 1: Application of usability engineering

Test	Test Purpose and Description
	to medical devices," and IEC/TR 62366-2:2016, "Medical devices - Part 2: Guidance on the application of usability engineering to medical devices." A total of 20 participants were included in the human factors and usability study, including fifteen (15) surgeons with relevant surgical experience on nerve repair, including hand surgeons, plastic surgeons, orthopedic surgeons, and podiatrists and five (5) surgical scrub nurses. The surgeons were independently recruited through a market research agency and had no prior knowledge or relationship with the sponsor and were evaluating the product for the first time. The surgeons assembled the allay Nerve Cap and then performed the simulated surgical procedure from removal of the device from the packaging, preparation of the dual-component applicator system, delivery of the hydrogel in situ into the Cap Form around an artificial nerve, and removal of the Cap Form with two different nerve sizes following the Instructions for Use. The scrub nurses were evaluated for their ability to assemble the device in preparation for delivery in the surgical site. The human factors and usability assessment demonstrated that the allay Nerve Cap and proposed Instructions for Use could be followed without any use errors and the use time of < 5 minutes was achieved with all users. All surgeons could perform all critical tasks (100%, n=15/15) related to preparing the device and delivering the hydrogel around different nerve sizes without any failures or use-related errors.

PERFORMANCE TESTING – ANIMAL

Two animal studies were performed to evaluate the in vivo safety and effectiveness and biocompatibility of the allay Nerve Cap.

Good Laboratory Practice (GLP) Rat Sciatic Nerve Transection Study

A GLP rat study was designed to evaluate the safety and performance of the sterile, final finished allay Nerve Cap after delivery in situ in a clinically relevant nerve transection injury model at 4 weeks and 3 months following implantation. Following nerve transection, the allay Nerve Cap was delivered in situ around the cut end of the rat sciatic nerve per the proposed Instructions for Use. The safety and performance of the allay Nerve Cap was compared with the cleared Polyganics Innovation BV NeuroCap Nerve Capping Device (K152684) in the control group. In addition, a negative control procedure, a transected nerve alone was included in the GLP rat study as a third group. The study captured outcomes both in-life and terminally to evaluate the safety and performance of the device in comparison to the two control groups.

The study demonstrated a benefit of the allay Nerve Cap on histologic, gross, and

behavioral assessments to support the intended use of the product to reduce the risk of neuroma formation (0%) and to help restore normal sensorimotor function. Overall, the hydrogel preparation and delivery were adequate with a total procedure time under two minutes. The hydrogel provided a transparent cover around the end of the nerve for the duration of the study with no evidence of axonal escape from the nerve stump into the surrounding muscle and scar tissue. There was no evidence of device migration.

The allay Nerve Cap has comparable safety to the Polyganics Innovation BV NeuroCap Nerve Capping Device (K152684) control for tissue response (non-irritant, non-neurotoxic), animal health, body weights, clinical and neurological observations, autotomy scores, and clinical pathology. The allay Nerve Cap also has comparable safety to the negative control (transection only) for these outcomes as well, with the exception that it is a slight irritant relative to the negative control group, consistent with the presence of a minimally degrading biomaterial implant at the site of implantation. No device related adverse effects were observed throughout the study.

Non-GLP Implantation Study on Intact Rabbit Sciatic Nerve

A chronic study was designed to evaluate the safety and performance of the sterile, final finished allay Nerve Cap after delivery in situ in a clinically relevant intact nerve model in a rabbit at 6 months and 8 months following implantation. The study objective was to evaluate the biocompatibility of the allay Nerve Cap over a chronic time frame during device absorption and clearance. The acceptance criteria are that the hydrogel, including partially or substantially degraded hydrogel, has (a) acceptable biocompatibility and does not cause an adverse inflammatory response to the nerve or the surrounding tissue and (b) the device should have similar biocompatibility to the comparator control group, recognizing that the control article is non-degradable and therefore a degradation-mediated response to the material is absent. The acceptance criteria were evaluated through clinical assessments, gross pathology of the implant, histopathologic assessment, and systemic assessment (clinical chemistry, hematology, and urinalysis).

A total of fourteen (14) New Zealand white rabbits received bilateral implants with the allay Nerve Cap (n=14) around the left sciatic nerve and a silicone cuff with slit (n=14) around the right sciatic nerve. In brief, after sciatic nerve exposure, the nerve was placed inside the temporary silicone Wrap Form (identical to a Cap Form but with an entrance and an exit) and the allay Nerve Cap hydrogel was delivered around the nerve to form a compliant hydrogel wrap. The silicone Wrap Form was then removed and discarded. The rabbit sciatic nerve model was selected as an acceptable small animal model for ISO 10993-6 implantation testing that provides a larger diameter (2 to 3 mm) clinically relevant nerve in which to assess the long-term in vivo persistence and degradation behavior of the hydrogel, the local tissue response at the site of implantation of the degrading hydrogel, the absence of neurotoxicity, the absence of compression of the nerve, and an assessment of the systemic toxicity as measured through clinical pathology, hematology, and urinalysis.

All animals were in good health over the course of the study and survived to the

scheduled study terminal time points. The allay Nerve Cap was successfully delivered in one or more layers around the rabbit sciatic nerve in the Wrap Form in all animals (n = 14). The hydrogel formed a transparent circumferential layer around the nerve. No adverse neurologic or behavioral effects such as lameness, dropped hocks, gait abnormalities were observed at any time. All animals gained an appropriate amount of weight over the study and were in good body condition at the time of termination. There were no apparent clinical signs related to the allay Nerve Cap or silicone cuff observed during the study. The animals were able to ambulate normally and there were no signs of pain, autotomy or overt signs of infection. Similarly, no neurologic abnormalities were noted post-implant or any other observations that could be attributed to the device or procedure. The clinical pathology and urinalysis supported the clinical findings of normality at study term. Hematology, serum chemistry and coagulation parameters were all normal and there were no trends indicative of a pathological pattern.

LABELING

The labeling includes instructions for use for the physician and satisfies the requirements of 21 CFR § 801.109 for prescription devices. The labeling also includes:

- Detailed description of the device technical parameters and all components.
- Detailed instructions on proper device preparation and implantation.
- A shelf life.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of an in situ polymerizing peripheral nerve cap and the measures necessary to mitigate these risks.

Risks to Health	Mitigation Measures
Pain • Decrease or increase in nerve sensitivity • Ineffective treatment leading to symptomatic neuroma formation	In vivo performance testing
Adverse tissue reaction	Biocompatibility evaluation Polymerization process characterization
Tissue injury (thermal/mechanical) resulting from: • Thermal/mechanical effects • Use error • Device migration	In vivo performance testing Polymerization process characterization Human factors/usability testing Non-clinical performance testing Labeling
Infection	Sterilization validation Shelf life testing Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the in situ polymerizing peripheral nerve cap is subject to the following special controls:

(1) A characterization of the following chemical characteristics of the polymerization process must describe how the in situ application of the precursor materials will result in a consistent final device. All chemically relevant changes to parts (iii)-(vi) below are determined to significantly affect the safety or effectiveness of the device (21 CFR 807.81(a)(3)(i)) and must be described in a premarket notification:
   (i) The technical specifications of the precursor materials including the chemical formulation, purity, particulate matter, appearance, molecular weight, pH, and viscosity;
   (ii) The delivery mechanism of the precursor materials to the site of application;
   (iii) The polymerization mechanism and polymer structure;
   (iv) The intermediates or side products produced;
   (v) The degradation pathway and degradants; and
   (vi) The contribution of any initiators or quenchers to the polymer, intermediates or side products, and degradants.

(2) Non-clinical performance testing data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be evaluated:
   (i) A characterization of the polymerization process must be provided that describes how the in situ application of the precursor materials will result in a consistent final device. Chemically relevant changes to the characteristics below are determined to significantly affect the safety or effectiveness of the device (21 CFR 807.81(a)(3)(i)) and must be described in a premarket notification:
      (A) The polymerization mechanism and polymer structure;
      (B) The intermediates or side products produced;
      (C) The degradation pathway and degradants; and
      (D) The contribution of any initiators or quenchers to the polymer, intermediates or side products, and degradants.
   (ii) Degradation testing of the polymerized device must be performed under simulated clinical use conditions.
   (iii) Mechanical integrity testing including elastic modulus, compression, swelling, and rebound testing must be performed.
   (iv) Physico-chemical testing of the polymerized device (i.e., dimensions, pH, molecular weight, purity, particulate matter, viscosity, density, dissolution time, gel time, reaction temperature) must be performed.
   (v) Polymerized device deliverability testing with any applicator(s) or delivery system(s) must be performed.

(3) Human factors/usability testing must demonstrate that the intended user(s) in the intended use environment can correctly and safely use the device following the instructions for use.

(4) The tissue-contacting components of the precursor materials, intermediate or side products, degradants, and final polymerized device must be demonstrated to be biocompatible.

(5) Performance data must demonstrate the sterility of all tissue-contacting components of the device and any delivery systems.

(6) Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

(7) In vivo performance testing must demonstrate that the device performs as intended to reduce the risk of the development of symptomatic neuroma and assess tissue injury, device durability, device migration, device preparation and deliverability, and all adverse effects.

(8) Physician labeling must include:
   (i) Detailed instructions on proper device preparation and implantation.
   (ii) Detailed description of the device technical parameters and all components.
   (iii) A shelf life.

BENEFIT/RISK DETERMINATION

The risks of the device are based on data collected in nonclinical laboratory and animal studies described above. The risks of the allay Nerve Cap are adverse tissue reaction, tissue injury, decrease or increase in nerve sensitivity, infection, or pain. These risks could occur from a device that is not biocompatible, a device not provided sterile, inadequately formed polymer hydrogel, device migration, nerve compression, or improper device use or use error.

The probable benefits of the device are also based on data collected in nonclinical laboratory and animal studies as described above. The benefits of the device are demonstrated in the animal study that showed there were no animals with neuroma formation (0%) within 3 months of implantation of the allay Nerve Cap, which is the time period most likely for symptomatic neuromas to form in human patients.[7] The animal study and nonclinical laboratory testing further demonstrated that the allay Nerve Cap remained intact during the 3-month period associated with neuroma formation to act as a physical barrier to separate the peripheral nerve end from the surrounding environment. The animal study also demonstrated the animals were able to restore normal sensorimotor function after implantation of the allay Nerve Cap.

Additional factors to be considered in determining probable risks and benefits for the allay Nerve Cap include that there was no clinical performance data provided to support the risks and benefit of the allay Nerve Cap for its proposed indications for use. However, there has been a body of clinical evidence collected on the use of nerve cap devices to reduce the risk of the development of a symptomatic neuroma within the 3-month period following the primary peripheral nerve

[7] Karla M. C. Oliveira et al. "Time course of traumatic neuroma development." PLoS One, Jul 2018, Vol 13(7):e0200548. doi: 10.1371/journal.pone.0200548. PMID: 30011306; PMCID: PMC6047790.

repair procedure that can be used to support the effectiveness of the allay Nerve Cap.[8] There is uncertainty regarding whether the allay Nerve Cap will result in functional benefit to human patients since it is difficult to fully assess pain and functional outcomes in animals and whether this data is translatable to human patients. The provided animal studies primarily focused on histological changes rather than behavioral changes in the animals. The animal study was able to support the proposed indications for use of the allay Nerve Cap to reduce the risk of development of a symptomatic neuroma because none of the animals implanted with the allay Nerve Cap exhibited neuroma formation within 3 months.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> The allay Nerve Cap is indicated for use in adults aged 22 years or older as a physical barrier to separate the peripheral nerve end from the surrounding environment to reduce the risk of the development of a symptomatic neuroma.

The probable benefits outweigh the probable risks for the allay Nerve Cap. The device provides benefits, and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the allay Nerve Cap is granted and the device is classified under the following:

> Product Code: SBG
> Device Type: In situ polymerizing peripheral nerve cap
> Class: II
> Regulation: 21 CFR 882.5260

[8] Amy M. Moore and Susan E. Mackinnon. "Nerve Repair and Transfers from Hand to Shoulder, Hand Clinics." Clinic Review Articles, May 2016, Vol 32(2), Elsevier, ISBN 9780323445191.