SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Epicardial Pacing Lead

Device Trade Name: Myopore Sutureless Myocardial Pacing Lead

Device Procode: DTB

Applicant's Name and Address: Greatbatch Medical
2300 Berkshire Lane North
Minneapolis, MN 55441

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P130012

Date of FDA Notice of Approval: April 30, 2015

The Myopore Sutureless Myocardial Pacing Lead has been commercially available since August 9, 1991 when it was first cleared by FDA under K910528. P130012 has been submitted in response to the Final Rule issued July 6, 2012 in the Federal Register Volume 77 Number 130, Docket No. FDA-2011-N-00505, requiring premarket approval of marketed pre-amendment Class III cardiovascular permanent pacemaker electrode, product code DTB. A product affected by this Rule is the Myopore Lead. A combination or post market experience data, relevant literature, and in-vitro bench testing has been reviewed to demonstrate a reasonable assurance of safety and effectiveness for the Myopore Lead.

II. INDICATIONS FOR USE

The sutureless myocardial lead is indicated for use when ventricular epicardial attachment is required, or when a transvenous lead cannot provide effective pacing. This type of lead is useful in situations where it is required that the potential for lead dislodgement be diminished or pacing and/or sensing will be established subsequent to open heart surgery.

III. CONTRAINDICATIONS

The Myopore Sutureless Myocardial Pacing Lead is contraindicated for:

- Patients in which the ventricular myocardium is thin walled, suffused with fat or fibrotic tissue, or is heavily infarcted
- Atrial implantation due to helix length (3.56 mm) being longer than the average atrial wall thickness (0.5 – 3.55 mm)

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Myopore Sutureless Myocardial Pacing Lead labeling.

V. DEVICE DESCRIPTION

The Myopore Lead (Models 511210, 511211, and 511212) is a bipolar lead consisting of a coaxial design with an inner conductor coil that is connected to the cathode and an outer conductor coil that is connected to the anode. The conductor coils are quadrafilar and constructed from MP35N, a nickel alloy comprised of 35% wt. Nickel, 35% wt. Cobalt, 20% wt. Chromium, and 10% wt Molybdenum. The coils are insulated with silicone rubber. The bipolar terminal assembly consists of a connector ring and pin made of 316L stainless steel. The terminal assembly is IS-1compatible. A depiction of the Myopore Lead is shown below in Figure 1.



Figure 1: Myopore Lead

The distal end of the lead consists of a molded silicone rubber lead head with a cathode electrode that is helical in design, as shown in Figure 2. Positive fixation to heart tissue is accomplished via the helically-formed distal electrode. The penetration depth of the cathode is 3.5 mm, which is screwed through the epicardium into the myocardium to establish electrical contact. The cathode (helix) is platinum iridium which is enhanced with a porous platinum black surface. A titanium anode electrode surrounds the cathode electrode. Woven polyester mesh adjacent to the anode electrode designed to promote fibrotic growth, which is intended to provide chronic fixation.

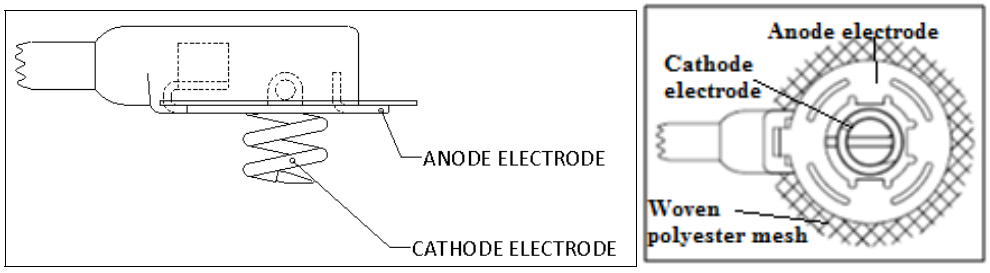


Figure 2: Bipolar Lead Head Side View (left), Bottom View (right)

The Myopore Bipolar Lead is available in three lengths (25 cm, 35 cm, and 54 cm) as listed in Table 1. The different lengths offer the physician options based on patient anatomy and system needs.

Table 1: Myopore Bipolar Leads Model Numbers

Model Number	Pacemaker Lead Connector Size	Lead Length
511210	IS-1 Bipolar	25 cm
511211	IS-1 Bipolar	35 cm
511212	IS-1 Bipolar	54 cm

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Patients who are eligible for epicardial leads have indications that require rhythm management which includes bradyarrhythmias and heart failure. Aside from pacing, there are no viable alternative procedures for treatment of bradyarrhythmias. There are alternatives or adjunct procedures for some heart failure patients, each with advantages and disadvantages. The present established therapies for the treatment of heart failure and the associated signs and symptoms include pharmacological therapy, heart transplantation, other surgical procedures, or active implantable cardiac resynchronization therapy. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Myopore Sutureless Myocardial Pacing Leads have been commercially available in a bipolar configuration in the United States since 1991 via 510(k) clearance. The Myopore Leads have been marketed in the European Union (CE Mark) since 1996 and in Canada under a Medical Device License, which was granted by Health Canada in 2011. Since 2005, approximately 50,000 bipolar epicardial leads manufactured by Greatbatch Medical (and its predecessors) have been sold.

In addition to these geographies, Greatbatch Medical partners with distributors to provide the Myopore Lead worldwide.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse effects (e.g., complications) associated with the use of the Myopore Sutureless Myocardial Pacing Lead identified from the available post-market safety data (including complaints and reported adverse events), approved device labeling for other epicardial leads, and published scientific literature meta-analysis results. The adverse effects include: (1) those associated with any surgical procedure; (2) those associated with the epicardial lead placement procedure; and (3) those associated with the use of an epicardial lead, including the Myopore Sutureless Myocardial Pacing Lead. In addition to the risks listed below, there is the risk that the pacing therapy-mediated by the epicardial lead may not be effective in relieving symptoms, or may cause worsening of symptoms. Additional intervention may be required to correct some of the adverse effects.

1. Risks associated with any surgical procedure include: abscess; cellulitis; excessive fibrotic tissue; wound dehiscence; wound, local or systemic infection; wound necrosis; edema; inflammation; foreign body reaction; hematoma; seroma; thrombosis; ischemia; embolism; thromboembolism; hemorrhage; thrombophlebitis; adverse reactions to anesthesia; hypertension; pulmonary complications; organ, nerve or muscular damage; gastrointestinal or genitourinary compromise; seizure, convulsion, or changes to mental status; complications of pregnancy including miscarriage and fetal birth defects; inability to resume activities of daily living; and death.

2. Risks associated with epicardial lead placement procedures: arrhythmia; myocardial injury or irritation; cardiac perforation; vascular damage; cardiac tamponade; pneumothorax; hemothorax; excessive bleeding; pericardial injury; and death.

3. Risks associated with use of epicardial leads, including the Myopore Sutureless Myocardial Pacing Lead: dislodgement; elevated thresholds; loss of pacing and/or sensing due to dislodgement or mechanical malfunction; exit block; extracardiac stimulation including muscle or nerve stimulation; induced arrhythmias; breakage of the lead insulation, breakage of lead conductor or helix; vascular dissection or perforation; myocardial perforation or erosion; and poor connection to the implantable pulse generator.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Bench Testing performed on the Myopore Leads is summarized in the Table 2.

Table 2: In-Vitro Design Verification Testing

Test Name	Purpose	Method	Acceptance Criteria	Results
Environmental Testing				
Ethylene Oxide (EO) Sterilization	The lead, accessories, inner tray, outer tray and any attached labels shall be capable of up to three (3) ethylene oxide (EtO) sterilization cycles.	Test units were exposed to multiple sterilization cycles to ensure the devices function as intended should they undergo the maximum allowable exposures to sterilization conditions while in distribution. The lead packages were preconditioned at a temperature of 100 ± 10° F with relative humidity of 50% for 20 – 30 hours. After sterilization the lead packages were exposed to aeration at 100 ± 10° F for 24 – 48 hours. This process was repeated for a minimum of three (3) sterilization cycles for all samples in accordance with the device specification	All samples must pass. EO Sterilization is pre-conditioning for subsequent design verification tests.	PASS
Thermal Shock	The lead and its accessories shall be capable of handling storage temperatures between 150ºF (66ºC) and -35ºF (-37ºC).	Condition samples per the following temperature exposures: Cycle: • Start at 25°C (± 5°C) • -37°C (+0/-5ºC) for 30 minutes (+5 min./-0 min.) • 66 ºC (+5ºC/-0 ºC) for 30 minutes (+5 min./-0 min.) • 25 ºC (±5ºC) for 60 minutes minimum Perform the above cycle 5 total times at a ramp rate of 1-2 ºC per minute.	All samples must pass. Thermal Shock is pre-conditioning for subsequent design verification tests.	PASS

Design Verification Testing				
Cross Circuit DC Resistance	Evaluate electrical continuity and verify leads meet DC resistance requirements.	The lead resistance was measured between each of the electrodes and connectors, using a maximum source current of 1 mA. The following were measured using a digital multimeter: IS-1 Connector Pin to Helix Electrode (cathode), and IS-1 Connector Ring to Anode Plate.	511210 (25 cm) Pin to helix resistance ≤ 30.0 Ω Ring to anode plate ≤ 45.0 Ω 511211 (35 cm) Pin to helix resistance ≤ 30.0 Ω Ring to anode plate ≤ 55.0 Ω 511212 (54 cm) Pin to helix resistance ≤ 43.0 Ω Ring to anode plate ≤ 84.0 Ω	PASS
Connector Flex	Evaluate connector flex fatigue and verify leads can withstand flexural stresses that may occur after implantation due to interaction between lead connector and pulse generator header.	In accordance with EN 45502-2-1, the samples were flexed ± 45° at a rate of 2 Hz for a minimum of 82,000 cycles. The resistance was monitored during testing to ensure that electrical function was maintained.	82,000 cycles at ± 45° at 2 Hz	PASS
Lead Body Flex	Evaluate lead body flex fatigue and verify lead bodies can withstand flexural stresses that may occur after implantation.	In accordance with EN 45502-2-1, the lead body was flexed at 90°, +0°, -5° at a rate of 2 Hz for a minimum of 47,000 cycles. The resistance was monitored during flexing to ensure that electrical function was maintained.	47,000 cycles at ± 90° at 2 Hz	PASS

Connector Deformation – Insertion Withdrawal	Evaluate functional compliance to IS-1 standards for maximum insertion and withdrawal forces after being exposed to the forces of tightening a setscrew.	A setscrew with both pin and ring contact was torqued to 0.15 Nm ± 0.01 Nm (24 ±1 oz-in). All torque was removed on contact until the connector was in a position to be removed without interference of the setscrews. The lead connector was fully seated into the fixture by grasping the lead approximately 2.5 cm from the tip of the pin. The peak insertion and withdrawal force in dry and wet conditions was measured and recorded. Electrical continuity of the lead was then verified.	Insertion/Withdrawal forces ≤ 14 N (3.14 lbf) (wet and dry)	PASS
IS-1 Electrical Impedance (Offset)	Evaluate leakage current and verify lead meets electrical impedance requirements in accordance with IS-1 standard.	The lead was inserted into an offset gage and submerged into saline solution at 37° C. Setscrews were tightened and 250 mV were applied to the lead at a frequency of between 60 and 120 Hz while impedance across lead terminals was measured. The test was repeated after a 10 day soak.	≥ 50 KΩ	PASS
Lead Sensing Impedance	Evaluate leakage current and lead sensing impedance.	The lead was placed in a fixture as described in EN 45502-2-1 Section 6.2.3. The resistance of the lead (sensing impedance) was measured.	511210 (25 cm) 58 - 800 Ω 511212 (54 cm) 116 – 800 Ω	No unexpected impedance values were measured
Lead Pacing Impedance	Evaluate leakage current and verify pacing impedance measurements.	The lead is placed in a fixture as described in EN 45502-2-1 section 6.2.2 and the lead current is determined by measuring the voltage drop across the resistor. Lead pacing impedance is calculated.	511210 (25 cm) 58 - 800 Ω 511212 (54 cm) 116 – 800 Ω	No unexpected impedance values were measured

Composite Tensile Integrity (Lead Durability)	Evaluate composite lead tensile strength and verify leads can withstand tensile forces that can occur after implantation.	The lead was soaked for 10 days and then subjected to a 5N axial force for one minute. DC resistance was measured and hypot testing was performed to verify electrical continuity. A subset of leads was then cut into proximal and distal sections which were stretched to failure.	≤ 5% length change Pin to helix resistance ≤ 43.0 Ω Ring to anode plate ≤ 84.0 Ω Distal and proximal portions of lead must have a tensile strength > 1.12 lb	PASS
Distal Tip Flex Fatigue	Verify that the leads can withstand the flexural stresses that can occur at the transition between the distal portion of the lead and the lead body.	In accordance with EN 45502-2-1, a 100 ± 5 g weight was attached to the lead body. An initial resistance reading of the lead was taken. The samples were then flexed ± 45° at a rate of 2 Hz for a minimum of 82,000 cycles. A final resistance was taken to confirm no conductor fractures.	The distal portion of the lead must maintain continuity during the duration of the testing.	PASS
Long-Term Flex Fatigue	Verify the distal portion of the lead maintains continuity after 400 million cycles equivalent to the number of heartbeats after 10 years of implantation.	The leads were flexed in a fixture under continuous monitoring until the lead underwent 400 million flex cycles. DC resistance was recorded throughout the duration of testing and a final measurement was taken once the test was completed.	The distal portion of the lead must maintain continuity during the duration of the testing.	PASS
Corrosion Resistance	Verify the materials of the lead, after being exposed to processing, do not show evidence of corrosion.	The lead was subjected to a ± 5V square wave signal at 2 kHz in 0.9% saline solution for 55 hours. The lead was then inspected at 10X magnification to examine the metallic parts for evidence of corrosion.	No trace of corrosion on the immersed metallic parts when viewed at 10X magnification. Pin to helix resistance ≤ 43.0 Ω Ring to anode plate ≤ 84.0 Ω	PASS

IS-1 Dimensional Verification	Evaluate lead dimensions and verify lead connector conforms with IS-1 standard.	Measure dimensions as defined in ISO 5841-3 using appropriate calibrated metrology equipment.	The connector shall meet IS-1 dimensional requirements per ISO 5841-3:2000.	PASS
FasTac Introducer Compatibility	Evaluate compatibility with all accessories and to verify the FasTac introducer is compatible with the lead.	While holding the introducer perpendicular to the heart, the electrode was firmly advanced into bovine heart tissue and rotated 2.25 turns in a clockwise direction. The lead was then released from the FasTac Introducer. After simulated tunneling, the lead was reloaded into the FasTac Introducer and removed.	The FasTac Introducer shall be capable of gripping and releasing the Myopore Lead through 6 cycles of simulated placement/removal without damaging the Myopore Lead.	PASS
Lead Tunneler Compatibility	Evaluate compatibility with all accessories and to verify the lead tunneler is compatible with the lead.	The lead connector pin was firmly seated in the tunneler tool accessory. The lead was then carefully removed from the tunneler tool.	The tunneler tool shall allow insertion and removal of the Myopore Lead pin through 6 cycles of simulated placement/removal without damaging the Myopore Lead.	PASS
Polarization Potential	Evaluate polarization potential and verify helix electrode polarization functions with known commercially available pulse generator wave function.	The lead is exposed to a pulse generator wave function to determine the resulting polarization of the device. The distal portion of the lead is submerged into a saline bath between two titanium plates. A wave generator is connected to the test setup in three configurations (tip to ring, tip to indifferent electrode, and ring to indifferent electrode) and resulting polarization is measured.	Polarization potential was assessed for characterization.	No unexpected values were measured

Particulate Testing	Evaluate particulate and verify that any part of the active implantable device intended to be in contact with body fluids shall cause no unacceptable release of particulate matter.	The samples were tested according to EN45502-2-1.	Average count of particles from a specimen compared to the reference sample shall not exceed 100 per ml greater than 5 µm and 5 per ml greater than 25 µm.	PASS
Defibrillation Voltage	Evaluate lead insulation function and to verify defibrillation of the patient will not permanently affect the device	The lead is attached to a circuit that includes a 300 ohm resistor, voltage generator and resistors representing inductance and defibrillation pulse generator in ohms. The lead is submerged in a saline bath and testing is conducted that subjects the lead to 104 V ±5%, representing a defibrillation device. Three voltage pulses are completed with positive polarity followed by three voltage pulses of negative polarity. After simulated defibrillation device exposure, units are evaluated for voltage resistance to ensure product still meets specification.	The insulation between conductors must withstand 1,000 VDC without electrical breakdown.	PASS

Biocompatibility testing performed on the Myopore Leads is included in Table 3. The materials used in the Myopore Sutureless Myocardial Pacing Lead are well-known and have a safe history of use with no known biocompatibility concerns.

Table 3: Biocompatibility Tests Performed

Biological Effect	Test Method	Results
Cytotoxicity	ISO MEM Elution Assay with L-929 Mouse Fibroblast Cells	PASS
Sensitization	ISO Guinea Pig Maximization Sensitization Test	PASS
Irritation/Intracutaneous Reactivity	ISO Intracutaneous Reactivity Test	PASS
Acute Systemic Toxicity	ISO Acute Systemic Injection Test	PASS
	Materials Mediated Rabbit Pyrogenicity	PASS
Subchronic Toxicity	Subchronic Toxicity Test (Multi-Dose)	PASS
Genotoxicity	Bacterial Mutigenicity	PASS
	In vitro Mouse Lymphoma Assay	PASS
Implantation	ISO Muscle and Subcutaneous Implantation Study in Rabbits	PASS

B. Animal Studies

A sub-chronic (up to 90 day) GLP Study was performed in the canine model. The purpose of this study was to evaluate (1) safety through gross, histological and fluoroscopic evaluation and (2) electrical performance through sensing, pacing, impedance, and threshold measurements. Canines (n=7) received 1 lead each and were evaluated for 90 day period. Interim follow up conducted at 7, 14, 21, 28, 60, and 90 days post implant. A necropsy study was conducted at termination. There were no adverse events or clinically significant findings at all time points for hematology, serum chemistry, histology, and pathology. Devices were electrically functional.

C. Additional Studies

i. Packaging and Shelf Life Testing
Packaging validation studies, including packaging seal and integrity, and shelf life were conducted to demonstrate that the device packaging can maintain a sterile barrier, with a shelf life of three years.

ii. Sterility Testing
The Myopore Sutureless Myocardial Pacing Lead and components are sterilized in compliance with ANSI/AAMI/ISO 11135-1:2007 and EN556-1. Results from sterilization studies demonstrate that the Myopore Sutureless Myocardial Pacing Lead and components will maintain a Sterility Assurance Level (SAL) of 10^{-6}.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant did not perform a clinical study; instead, the applicant evaluated the safety, effectiveness and survivability of epicardial leads through a detailed meta-analysis of relevant clinical articles performed in a quantitative and pooled fashion. Data abstraction for the meta-analysis used standard abstraction forms defined *a priori* and was conducted by independent consultants. Data were compiled across all publications, and then converted into a Statistical Analysis System (SAS) dataset for storage and analysis. The analysis dataset combined the data extracted from 76 articles, contributing a total of 123 unique cohorts of subjects (78,776 patients), using at least 10,648 leads. Of the 123 unique cohorts, 85 summarized results for subjects who had received epicardial leads (4,814 patients). The pooled lead data covered 4,814 patients implanted with at least 5220 leads. The patients included in the analysis were from across the globe and represented a maximum follow-up of 38 years.

Data Analysis Methods

For all information extracted from the publications, values that were not reported remained missing in the analysis dataset. That is, if a publication did not mention any occurrences of a particular outcome, that outcome remained missing for all analyses (e.g. it was not assumed that there were zero occurrences of that event).
For each clinical outcome, a Forest plot was generated to present the outcome-specific estimates and corresponding 95% confidence intervals (CI). After plotting the outcome-specific estimates, a fixed effects model was executed to estimate event rates.

After the fixed effect model was executed, statistical heterogeneity across cohorts was assessed using the Q-statistic. The Q-statistic follows the chi-square distribution, and the corresponding p-value was reported for each calculation; a value ≤ 0.05 was considered statistically significant, and indicated significant heterogeneity of event rates across the published study cohorts.

In view of the differences expected between studies and in order to be conservative, a random effects model was used to determine pooled estimates. The methods of DerSimonian and Laird[i] were applied to calculate the pooled event rates. A Forest plot was generated using these random effects estimates and corresponding 95% CIs.

Meta-Analysis Limitations

The meta-analysis has methodological limitations that should be noted. As with most meta-analyses, there is inherent publication bias. That is, only studies that were published are included in the meta-analysis. Often, unsuccessful studies are not published, resulting in a potential bias in the results of a meta-analysis.

A potential weakness of this meta-analysis is the variability in study design among the included studies. While most studies were either prospective or retrospective cohort studies at a single center, the study population and timing of the studies varied and contributed to some heterogeneity.

It should also be noted that the publications covered a wide range of duration of follow-up, and loss-to-follow-up was rarely reported. Therefore, the estimated outcome rates and corresponding confidence intervals may carry some mis-estimation error that would be difficult to quantify.

Nonetheless, the meta-analysis spans a large time period of clinical investigations, performed independently in multiple geographies for a variety of clinical uses and using different adjunct pacing systems and implant procedures. Therefore, it is reasonable to conclude that the results of the meta-analysis adequately represent the pooled clinical experience with epicardial leads.

A. Safety and Effectiveness Results

1. Safety Results

   The analysis of safety was largely based on the detailed meta-analysis of the clinical articles, as described above. The key safety outcomes for this analysis are presented below.

   a. **Overall Patient Cohort Outcomes**

      The summary of the analysis highlights a pooled estimate of occurrence of all-cause death at 9.18% or 9.26% depending on the effects models used (Fixed or Random). Similarly, infection rates are estimated at 2.88%/2.88%. Any complications related to the implant of the lead and any medical reintervention to address complications are estimated at 22.90%/8.37% and 12.04%/12.04%, respectively. Focusing on lead-related issues, the pooled data suggest a lead failure rate of 9.76%/9.76%, lead fracture rate 4.24%/4.79%. Other electrical performance issues are assessed with estimates ranging from 0.54%/0.54% for extracardiac (phrenic or diaphragmatic nerve) stimulation to 7.80%/9.48% for exit block. The results of the homogeneity tests suggests that, overall, the two effects models are not significantly different. The outcomes rate presented support acceptable levels of safety and effectiveness for the use of epicardial leads, regardless if evaluated using a fixed or a random effects model. Figure 3 and Table 4 below show the results of this analysis.

Figure 3: Overall Outcome Estimates for Fixed and Random Effects Models

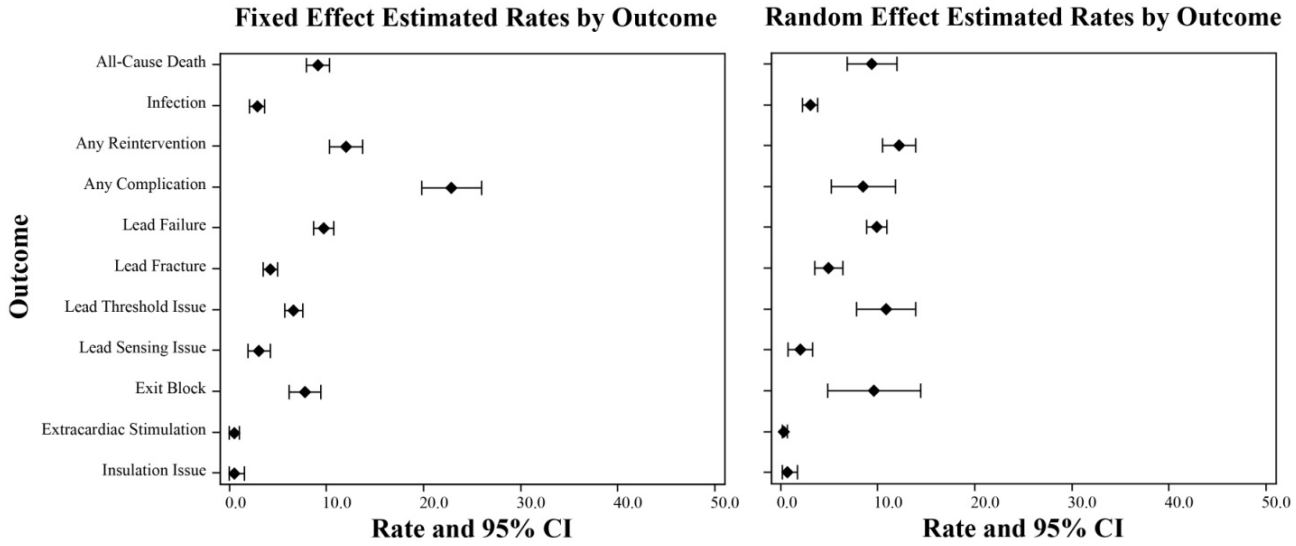


Table 4: Meta-Analysis of Outcome Rates

			Fixed Effect		Test of Homogeneity		Random Effect	
Study Group	**Cohorts**	**Subjects**	**Estimate (%)**	**95% CI**	**Q**	**P-value**	**Estimate (%)**	**95% CI**
All-Cause Death	46	2,401	9.18	(7.99, 10.37)	183.09	>0.99	9.26	(6.72, 11.81)
Infection	33	2,275	2.88	(2.13, 3.64)	21.427	0.08	2.88	(2.13, 3.64)
Any Reintervention	23	1,874	12.04	(10.31, 13.76)	-451.7	.	12.04	(10.31, 13.76)
Any Complication	20	1,159	22.90	(19.81, 25.98)	31.860	0.97	8.37	(5.05, 11.7)
Lead Failure	59	3,337	9.76	(8.73, 10.78)	-270.1	.	9.76	(8.73, 10.78)
Lead Fracture	36	2,575	4.24	(3.5, 4.98)	106.15	1.00	4.79	(3.36, 6.22)
Lead Threshold Issue	38	2,138	6.66	(5.72, 7.6)	312.87	>0.99	10.70	(7.67, 13.73)
Lead Sensing Issue	22	940	3.10	(1.95, 4.25)	32.353	0.95	1.89	(0.63, 3.15)

Exit Block	19	1,034	7.80	(6.16, 9.43)	120.33	>0.99	9.48	(4.72, 14.25)
Extracardiac Stimulation	11	540	0.54	(0, 1.08)	11.148	0.65	0.14	(0, 0.52)
Insulation Issue	1	184	0.54	(0, 1.61)	--	--	0.54	(0, 1.61)

Since the results of the Q statistic from the two effects models in this meta-analysis across all patient cohorts suggest there is no statistical evidence of differences between the two models, the following sub-analyses was presented using only the Random Effects model.

b. **Different settings: acute and chronic using a 30-day cut-off**
The surgical placement of the epicardial lead, though potentially minimally-invasive, may cause the patient to experience adverse events in the acute setting or the chronic setting, defined by a 30-day cut-off for acute and greater than 30 days for chronic events. These adverse events may be related to the implant procedure itself, dependent of the lead performance or independent of both and due to patient disease characteristics. Figure 4 and Table 5 below show the results of this analysis.

Figure 4: Outcome Estimates for Acute and Chronic Settings

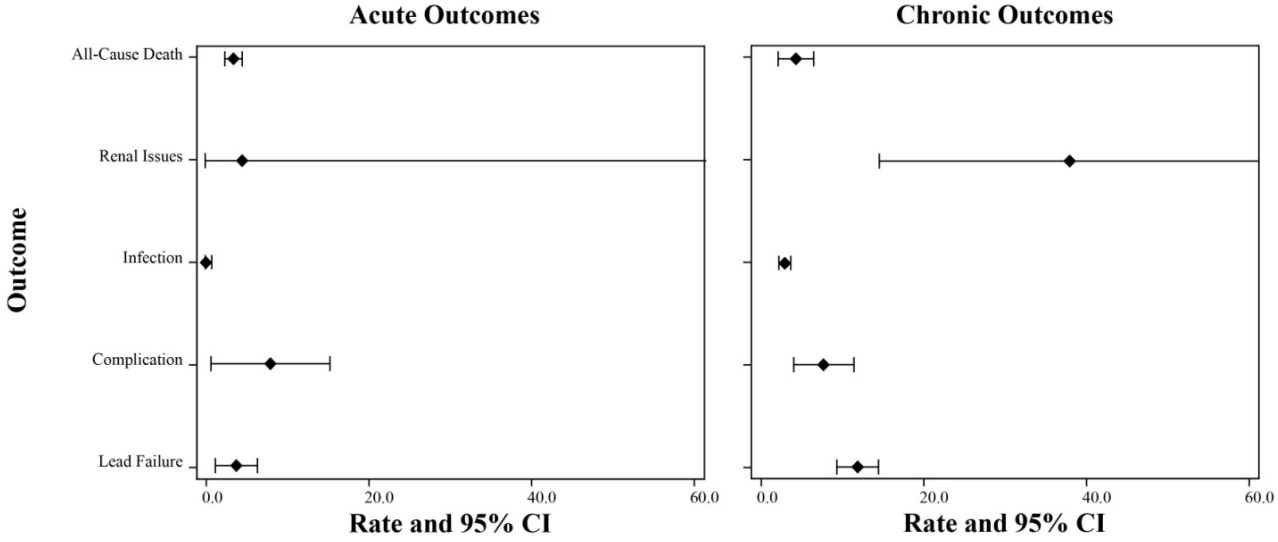


Table 5: Meta-Analysis of Acute and Chronic Outcome Rates

	ACUTE		ACUTE		CHRONIC		CHRONIC	
STUDY GROUP	**COHORTS**	**SUBJECTS**	**ESTIMATE (%)**	**95% CI**	**COHORTS**	**SUBJECTS**	**ESTIMATE (%)**	**95% CI**
All-Cause Death	28	1,553	3.80	(2.64, 4.96)	28	1,553	4.30	(1.94, 6.66)
Renal Issues	5	150	4.89	(0, 100)	5	150	40.00	(15.21, 64.79)
Infection	8	328	0.14	(0, 0.91)	33	2,275	2.83	(2.07, 3.58)
Complication	13	499	8.66	(0.78, 16.55)	20	1,159	7.91	(3.99, 11.84)
Lead Failure	12	479	4.14	(1.36, 6.92)	59	3,337	12.37	(9.69, 15.04)

The results do not raise any safety issues that would be unique to the acute or chronic settings. All-cause mortality and complications in both settings are comparable (3.80%/4.30% and 8.66%/7.91%, respectively). As would be expected, lead failure does increase in the chronic setting (4.14% to 12.37%). The estimated chronic renal failure is notably higher, however, the direct role an epicardial lead implant plays in the occurrence or exacerbation of chronic renal failure cannot be readily explained. It is notable that many patients referred to epicardial lead placement could have failed transvenous lead placement after a prolonged attempt (which is associated with significant contrast dye usage)[ii] or have an underlying disease with kidney dysfunction (common in heart failure patients). Aside from the considerations relative to renal complications, the data does support an acceptable level of safety in the acute and chronic settings.

c. **Different study follow-up duration: short and long follow-up using a two-year cut-off**

The clinical literature reviewed had varied levels of follow-up for patients with epicardial leads. In order to elucidate any potential impact that the follow-up period may play in the overall estimates for product safety and performance characteristics, an analysis was conducted to compare two cohorts dichotomized over a follow-up cut-off of 2 years. Figure 5 and Table 6 below show the results of this analysis.

Figure 5: Outcome Estimates for Short and Long Term Follow-up Cohorts

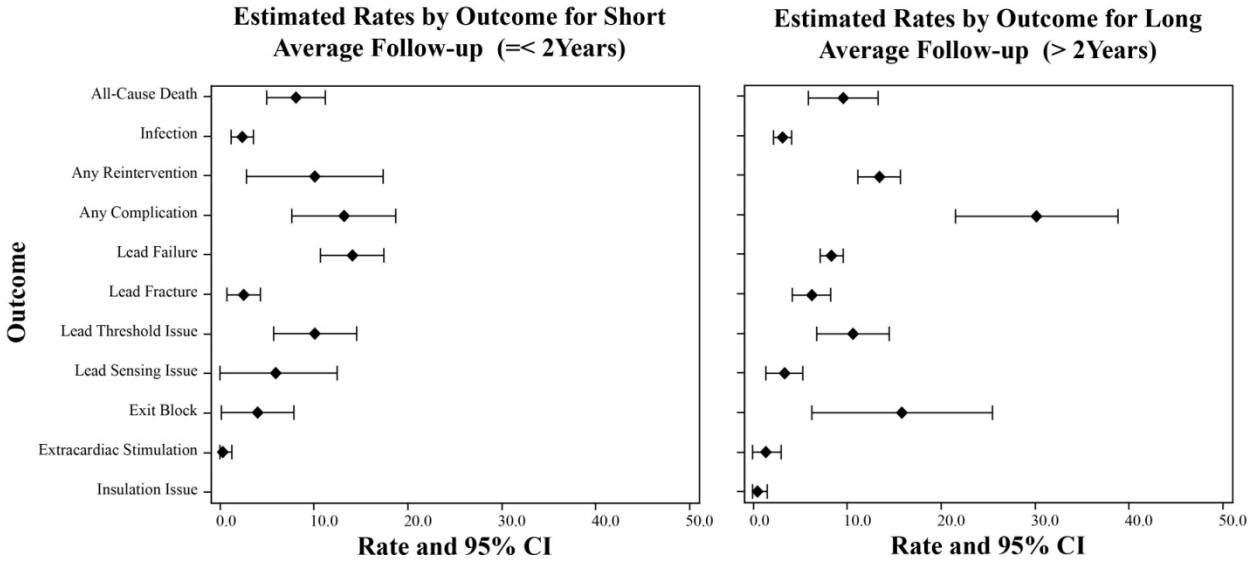


Table 6. Meta-Analysis of Outcome Rates

	Short Duration (≤2 Yrs)		Short Duration Random Effect		Long Duration (>2 Yrs)		Long Random Effect	
Study Group	**Cohorts**	**Subjects**	**Estimate (%)**	**95% CI**	**Cohorts**	**Subjects**	**Estimate (%)**	**95% CI**
All-Cause Death	22	776	8.14	(5.01, 11.27)	24	1,625	9.67	(5.97, 13.38)
Infection	13	832	2.42	(1.22, 3.61)	20	1,443	3.19	(2.22, 4.17)
Any Reintervention	9	487	10.13	(2.86, 17.41)	14	1,387	13.52	(11.26, 15.78)
Any Complication	12	760	13.21	(7.68, 18.74)	8	399	30.26	(21.61, 38.9)
Lead Failure	27	1,209	14.10	(10.75, 17.45)	32	2,128	8.44	(7.19, 9.68)
Lead Fracture	12	829	2.54	(0.75, 4.33)	24	1,746	6.30	(4.24, 8.36)
Lead Threshold Issue	15	763	10.15	(5.72, 14.58)	23	1,375	10.72	(6.88, 14.56)
Lead Sensing Issue	7	190	5.93	(0, 12.47)	15	750	3.40	(1.44, 5.37)
Exit Block	12	418	4.03	(0.15, 7.9)	7	616	15.91	(6.3, 25.53)
Extracardiac Stimulation	8	362	0.30	(0, 1.32)	3	178	1.45	(0, 3.08)
Insulation Issue	--	--	--	--	1	184	0.54	(0, 1.61)

The meta-analysis results suggest that most safety measures are not affected by the mean study follow-up duration. Some estimates did change however; any complication increased (13.21% to 30.26%), lead failures decreased (14.10% to 8.44%) and lead fracture increased (2.54% to 6.30%). This finding is not surprising since some parameters would be expected to develop and increase (like lead fracture) over time. Lead failure decreases over time, largely due to the early contribution of acute lead failures that resolves with longer follow-up durations.

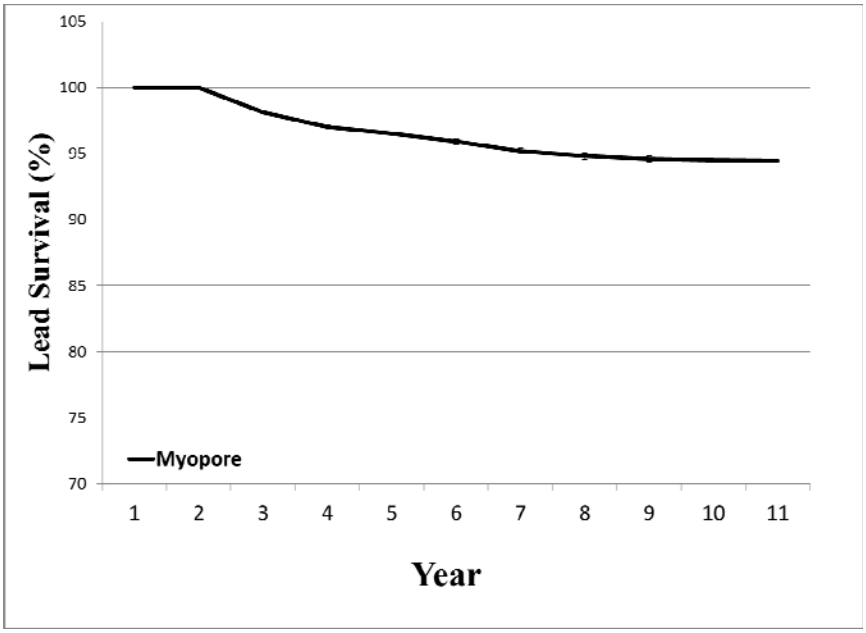
Aside from time-based changes, the data do not reveal any unexpected or previously unknown outcome concerns related to follow-up durations. Overall, the data supports an acceptable level of safety for the use of epicardial leads with short mean follow-up durations that is maintained over longer follow-up durations.

2. Effectiveness Results

The analysis of effectiveness was based on the survivability of epicardial leads over a period of fifteen (15) years. Key effectiveness outcomes are presented below.

Epicardial leads have been in clinical use with tenure of several decades. Therefore, the survivability analysis assessed from the reported literature would represent a real-world experience with epicardial leads. To represent the industry-wide epicardial lead survivability, an analysis was performed to derive a pseudo-survivability curve as a weighted average of actual reported epicardial lead survivability data from the clinical literature. This analysis included lead survival, freedom from failure, adjusted survivability and freedom from reintervention for lead replacement, explants or abandonment. Figure 6 shows the weighted average of lead survival with the corresponding 95% confidence intervals calculated from the literature. The numbers below the plot reflect the cohorts contributing to this analysis.

Figure 6: Average Survivability Plot for Epicardial Leads



The weighted average survival reported in the literature typically accounts for combined acute and chronic events for the duration of follow-up / retrospective review. In addition, it assesses the survivability at discrete time points based on the literature reporting survivability for the epicardial lead cohorts. The contribution of the cohorts was weighted to the size of the study and the sample size at study onset. Without the actual censored events, it is difficult to assess the actual cohort sample size contributing to the individual points.

These data are derived from studies conducted in the US as well as other countries. It is also derived from clinical literature using multiple epicardial lead manufacturers, across a long period of time, over multiple age cohorts, multiple disease cohorts, multiple follow-up periods and multiple implant techniques. Although the survivability analysis could not adjust for potential confounding variables, it is believed that when taking the scope, scale and long clinical tenure included in this analysis, the weighted average survival analysis would homogenize any peculiarities or nuances inherent to each clinical article when examined individually. In summary, the survivability data derived from this analysis suggests that epicardial leads have an acceptable level of device longevity under real-world conditions.

Therefore, the results of the meta-analysis indicate epicardial leads have an acceptable survivability profile over a period of 15 years.

B. **Financial Disclosure**

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and

arrangement of, any clinical investigator conducting clinical studies covered by the regulation. None of the authors of the studies in the literature used in the meta-analysis had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The applicant performed an extensive literature search and Myopore Lead product history analysis to further support the safety and effectiveness of these leads. The methods used are described below. The results from both of these approaches further support the safety, effectiveness and long term performance of the Myopore Lead, when used in a manner consistent with its labeling and intended use. The analyses also support a clinical benefit to risk determination that is favorable for the continued commercialization and use of the Myopore Lead.

A. An extensive clinical literature search was conducted to identify peer-reviewed articles that reported information regarding general epicardial lead safety, effectiveness and survivability. These articles were filtered by using systematic keywords for epicardial leads and reviewed using objective criteria. Exclusion criteria of the articles for the analysis were as follows:

- Articles with epicardial leads describing case studies, small studies with less than 10 subjects
- Journal not available
- Articles describing medical or surgical intervention or management unrelated to implanted epicardial ventricular leads
- Non-human studies including *in vitro*, cadaveric, animal, laboratory, modeling, simulation, genetic informational, or development
- Narrative reviews with no data about epicardial leads, comments, letters, other non-full length articles
- Articles describing only the use of atrial leads
- Studies describing use of an accessory or adapter.
- Studies describing use of temporary leads

The filtered articles were then reviewed by two subject matter expert reviewers and independently categorized into groups based on relevance of informational content:

- Group 1 represented highly relevant articles on the basis of rigorous testing and quantitative reporting on epicardial leads, including comprehensive lead disposition, disclosure of safety information, Kaplan-Meier curves, product survivability, etc. In this group, the peer-reviewed articles had epicardial leads as a central focus of the investigation.

- Group 2 represented articles of potential importance on the basis of anecdotal data content about epicardial leads, presented in less rigorous fashion or as a side note/finding in the article. In this group, the peer-reviewed articles mention

epicardial leads in the context of another focus for the investigation, or discuss leads with less quantitative rigor.

- Group 3 represented articles of minimal relevance to the clinical analysis on the basis of lack of relevant quantitative informational content on epicardial leads; or journal articles that were inaccessible. This group was excluded from all clinical evidence analysis.

The results of the relevant articles (n=76), spanning 3 decades from 1982 to 2012, were synthesized, summarizing the safety, effectiveness, electrical performance and survivability of epicardial leads.

B. A Myopore Lead product history analysis in terms of complaints, MDRs and recalls was completed to assess product performance over several years of clinical service, as well as a comparative evaluation of the safety and performance profiles of the Myopore Lead relative to substantially equivalent products with similarly long clinical use tenures. From 2005 to 2012, the FDA MAUDE database lists 63,578 total MDR entries under the query product code of "DTB". For that period, 282 MDRs were related to the Myopore lead. This translates to a Myopore MDR rate of 0.44% relative to the total industry-wide MDR number of 63,578. Note that this includes both the unipolar and bipolar configurations of the Myopore Lead. The results demonstrate that the Myopore Lead had low MDR rates that do not raise new concerns regarding product performance.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory Systems Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Epicardial leads are designed and intended to deliver effective pacing therapy for a long period of time, in patients that will require a lifetime of therapy. Therefore, a significant factor of lead effectiveness is its longevity (survivability) under clinical use conditions. The survivability analysis is derived from a broad and methodical clinical literature review and demonstrates strong performance defined by lead survivability, freedom from lead explants or intervention.

Another dimension of effectiveness for leads in general is the electrical performance. The pre-clinical testing shows that the Myopore Lead met the respective performance and design specifications. The clinical evidence presented shows electrical performance under clinical use conditions and the rate of re-interventions needed to remedy poor lead

performance or ineffective therapy delivery. The epicardial lead has an acceptable electrical performance in various cohorts where electrical performance could be influenced by underlying disease etiology and clinical application. This effective electrical performance is evident in the short term and over the long term. In total, the longevity and electrical data presented strongly supports an adequate effectiveness profile for the Myopore Lead.

B. Safety Conclusions

Epicardial leads are used as part of a system in patients indicated for pacing and require a surgical approach for lead implantation. Inherent to that procedure and the underlying clinical condition are safety concerns including death, infection, clinical complications and others. Safety concerns can be categorized as lead-related, procedure-related or independent of both. The clinical evidence provided demonstrates clinical safety by qualitatively describing the safety profile, by quantitatively analyzing the outcome rates and estimates of incidence of complications, by product history analysis accompanied by benchmarking to comparable products cleared for clinical use of identical indications. The clinical safety profile was also demonstrated in different subgroups and cohorts including follow-up time, acute vs. chronic impact, as well as longitudinal tracking of safety for over two decades. In total, these data strongly support a favorable clinical safety profile for the Myopore Leads.

C. Benefit-Risk Conclusions

The Myopore Lead provides an epicardial pacing option that can be placed with a minimally invasive approach, is bipolar and has active fixation. The overall performance is not based on an Investigational Device Exemption (IDE) Study but on twenty (20) years of market data and 70+ publications. The MDRs, literature, and the Meta-Analysis give the general sense that that the lead paces appropriately and provides the necessary benefit.

The risks include lead dislodgement or lead failure. This may require an additional invasive approach to place the new lead. Threshold increases and infection are also risks. If the patient is pacemaker-dependent and the lead suddenly fails, it could result in syncope, hemodynamic collapse or death. Risks such as perforation either acutely or after the procedure can also result in prolonged hospital stay or pericardial effusion with tamponade.

Although there is no IDE study to support this application, there are field complaints and publications spanning over two (2) decades that demonstrate this lead does has an acceptable safety profile. The Myopore Leadcan be placed minimally invasively with active fixation. Minimally invasive surgery carries less risk than a full thoracotomy to the patient. In addition, active fixation is a benefit to the patient who can avoid leads being sutured on to the epicardial surface.

Overall, the known benefits and the option to place a lead epicardially outweigh the risks of the lead which are well-known and well-documented in the literature.

D. Overall Conclusions

The data in this application provide a reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Based extensive pre-clinical verification, systematic literature review and meta-analysis study results, it is appropriate to conclude the following: A significant portion of the indicated patient population will achieve clinically significant results and the clinical benefits of the use of the Myopore Lead outweigh the risks associated with the device and surgical implant procedure, when used as indicated in accordance with the instructions for use.

XIV. CDRH DECISION

CDRH issued an approval order on April 30, 2015.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

[i] DerSimonian R, Laird N. (1986). Meta-Analysis in Clinical Trials. *Controlled Clinical Trials* 7:177-188.

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