SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: alfapump® System

Device Trade Name: alfapump® System

Device Procode: SDQ

Applicant's Name and Address:

Sequana Medical NV
Kortrijksesteenweg 1112
Sint-Denijs-Westrem
9051 BE

Sequana Medical US inc.
265 Franklin Street, Suite 1702
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Date(s) of Panel Recommendation: N/A

Premarket Approval Application (PMA) Number: P230044

Date of FDA Notice of Approval: December 20, 2024

Priority Review: N/A

Breakthrough Device: Granted breakthrough device status on January 16, 2019 because the subject device met the Breakthrough criteria.

II. INDICATIONS FOR USE

The alfapump® System is intended for single patient use only in adult patients with refractory or recurrent ascites due to liver cirrhosis. It is indicated for the removal of excess peritoneal fluid from the peritoneal cavity into the bladder, where it can be eliminated through normal urination.

III. CONTRAINDICATIONS

MRI Safety Information

- The alfapump® is MR unsafe.
- This diagnostic procedure is contraindicated due to possible movement of the alfapump®, damage to the pump circuitry, tissue damage in the vicinity of the alfapump® and/or catheter dislocation.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy is contraindicated because the environmental conditions entailed in this therapy are out of the defined range of use for the alfapump® System.

IV. WARNINGS AND PRECAUTIONS

Only trained users should use the alfapump® System. The hazards, warnings and precautions can be found in the labeling. Please refer to the The alfapump® System Instructions for Use for additional applicable warnings and precautions

V. DEVICE DESCRIPTION

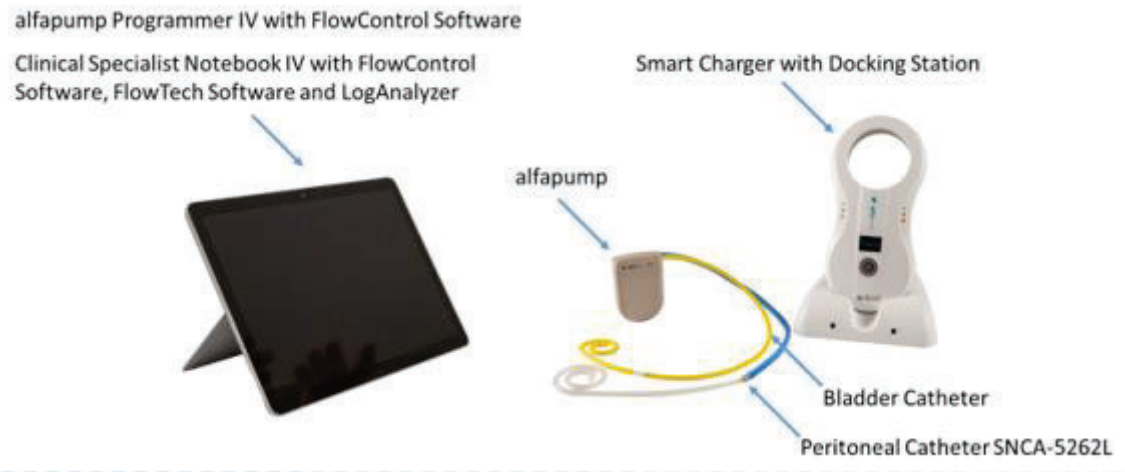
The alfapump® System is an implanted device with a rechargeable battery that is designed to slowly and continually transport ascites from the peritoneal cavity to the urinary bladder where it is eliminated by spontaneous urination. The implantable system components consist of a subcutaneously implanted pump and two catheters that connect to the pump. The volume of fluid to be removed and frequency of pump activity are set by the physician. The alfapump® System consists of:

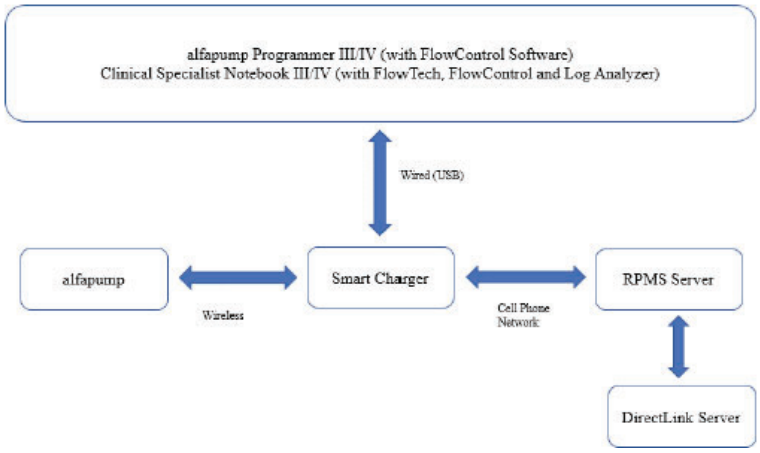
i. alfapump®
ii. Bladder Catheter
iii. Peritoneal Catheter SNCA-5262L
iv. Smart Charger and Docking Station
v. alfapump® Programmer IV (with FlowControl Software)
vi. Clinical Specialist Notebook IV (with FlowTech Software)
vii. Implant Accessories Catheter Locking Cap
- Peritoneal Catheter Extension
- Bladder Catheter Extension
- Catheter Extension Connector

viii. Implant Tools Introducer Kit
- Introducer Kit
- Tunneling rod

Figure 1 below illustrates the alfapump® System followed by a brief overview of each system component. The key performance requirements and specifications (hardware and software) of the alfapump® System are derived from applicable performance standards and product development lifecycle.

Figure 1 alfapump® System Components and Interfaces





As illustrated in **Figure 1** above, all individual components are interconnected and linked together through USB (wired) or wireless communication. All communication takes place through the Smart Charger, which serves as the primary interface for communication and charging of the alfapump®.

Figure 2 alfapump (with catheter connector)

As shown in **Figure 2**, the alfapump® is a single-use, sterile, implantable, and inductively charged gear pump. The pressure sensors within the pump monitor fluid movement to prevent pumping from an empty peritoneal cavity or overfilling the bladder. The pump has one inlet and one outlet connector for attachment of the Peritoneal Catheter and Bladder Catheter. The Bladder Catheter transports peritoneal fluid from the alfapump® to the bladder. The Peritoneal Catheter SNCA-5262L transports peritoneal fluid from the peritoneal cavity to the alfapump®, where it is pushed to the bladder through a Bladder Catheter. The catheters are fixed to the pump with a locking cap. On the exterior, two polyester patches are attached. The purpose of these patches is to promote fixation to the tissue in the subcutaneous pump pocket.

The alfapump®'s battery is inductively charged transcutaneously via the Smart Charger. The Smart Charger transmits power transcutaneously to and communicates via radiolink with the alfapump®.

Each time the patient charges the alfapump®, its pump data is automatically transferred to the Smart Charger. An integrated cellular modem allows for alfapump® performance data to be transferred to Sequana Medical over mobile phone network for analysis purposes only. The patient must bring the Smart Charger to each follow-up visit so the physician can transfer its pump data to the provided alfapump® Programmer III/IV (notebook/laptop) for review. The communication software on alfapump® Programmer III/IV enables physicians to:

- communicate with the implanted alfapump®;
- adjust the settings based on individual patient needs; and
- retrieve pump data via the patient's Smart Charger.

Please refer to the the alfapump® System Instructions for Use for additional details.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of refractory ascites. 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.

The alfapump® System is commercially available in the EU and has a CE Mark in accordance with the EU Medical Device Regulation (MDR) 2017/745. As part of the conformity with the EU MDR, a Clinical Evaluation Report (CER) is required to be maintained and updated on an annual basis. As part of this process, a systematic and state of the art literature review was conducted in February 2023 for both safety and performance of the alfapump® System covering the period July 2022 to February 2023 in accordance with the EU MDR for the CER.

A high-level summary of the relevant alternative practices and procedures for patients with refractory ascites is included in this CER and a summary of this information was extracted from this literature review and is included below. Additionally, only liver transplant treats the underlying etiology of ascites development, and thus, does prevent recurrence.

Large Volume Paracentesis

According to current guidelines, the standard treatment for refractory or recurrent ascites is repeated paracentesis to evacuate the ascites and the administration of albumin (8g/L of ascitic fluid extracted) when the volume of ascites removed exceeds 5 liters [1-3]. The requirement for repeated paracentesis leads to reduced patient quality of life and increases the risk of complications [4].

A possible complication associated with Large Volume Paracentesis (LVP) is paracentesis-induced circulatory dysfunction (PICD) syndrome, which is the result of further reducing effective arterial volume secondary to extracting a large volume of ascitic fluid. This syndrome is associated with a rapid re-accumulation of ascites, the development of renal dysfunction or dilutional hyponatremia, with a reduction in survival [5, 6]. The administration of albumin (as per the quantities mentioned above) is believed to prevent the occurrence of PCID in an important number of cases [7, 8]. Additional complications of ascites include peritonitis and incarceration of abdominal hernias [9].

Peritoneovenous Shunt

Currently, peritoneovenous shunt plays a minor role in the treatment of refractory ascites due to a higher risk of disseminated intravascular coagulation, sepsis, and heart failure [10]. Current evidence-based clinical practice guidelines recommend that in patients with refractory ascites with no other therapeutic options, peritoneovenous shunt should be performed after cautious assessments and obtaining informed consent. For patients with massive ascites with peritoneal dissemination abdominal-venous shunting is strongly recommended not to be performed, due to frequent and fatal complications [11].

Transjugular intrahepatic portosystemic shunt (TIPS)

In selected patients with refractory or recurrent ascites, a transjugular intrahepatic portosystemic shunt (TIPS) is an alternative to serial paracentesis [12]. Although this procedure has reported efficacy in the range of 45% to 63% [13], the therapy has several limitations, including the requirement for careful training to conduct the procedure, the attendant risks associated with the presence of the shunt such as hepatic encephalopathy, and the consideration that a substantial portion of patients with refractory ascites are not candidates for TIPS insertion [9]. The European Association for the Study of the Liver (EASL) guidelines caution that "careful selection of patients for elective TIPS insertion is crucial, as is the experience of the center performing this procedure. TIPS is not recommended in patients with serum bilirubin > 3 mg/dl and a platelet count lower than 75 x 109/L, current hepatic encephalopathy grade ≥2 or chronic hepatic encephalopathy, concomitant active infection, progressive renal failure, severe systolic or diastolic dysfunction, or pulmonary hypertension [2]."

Liver transplantation

Liver transplantation in patients with cirrhosis is still the long-term treatment of choice, and the definitive cure, in those with recurrent and refractory ascites who are candidates for transplantation, with overall survival greater than 85% at 1 year after transplantation [14, 15]. However, more than 40,000 cirrhosis patients die each year in the US from liver disease and only 6,000 liver transplants are performed each year. In addition, many patients with refractory or recurrent ascites do not qualify for a liver transplant or are at a lower tier on the transplantation waiting list [16].

The lack of sufficient donor organs for transplantation, poor quality of life, repeat paracentesis with albumin requiring repeated hospital visits and resulting in poor quality of life, and the fact that a significant proportion of patients with refractory ascites have contraindications to and/or would not benefit from TIPS highlight the need for new treatment options. The Sequana Medical alfapump® System can offer an alternative treatment option for cirrhotic patients with refractory or recurrent ascites that addresses a significant medical need for management of their disease that facilitates an alternative to LVP.

VII. MARKETING HISTORY

The alfapump® System received CE mark approval under 90/385/EEC (AIMDD) in 2011 and most recently the alfapump® System has been approved under the MDR (EU) 2017/745 in 2022. The alfapump® System is being actively marketed in Europe. There has been a total of over 420 commercial implants of alfapump® Systems from 2016 until September 30, 2023.

In summary, the alfapump® System has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the alfapump® System. For the specific adverse events that occurred in the clinical study, please see Section X below.

Potential adverse events (AE) which may be associated with the procedures required to place the device (including the procedure to place the catheters and pump and local and/or general anesthesia) include but are not limited to, the following:

- Adverse reaction to sedation, local or general anesthesia
- Pain
- Sore or irritated abdomen
- Bleeding
- Catheter track bleeding
- Wound dehiscence
- Injuries to the digestive tract during placement
- Injuries to blood vessels
- Abdominal wall haematoma
- Persistent leakage of ascitic fluid
- Peritonitis
- Urinary tract infections
- Cardiac or respiratory arrest connected to underlying medical problems

Potential adverse events (AE) that may be specifically associated with the alfapump® therapy include but are not limited to the following:

- Pump pocket
  - Hematoma
  - Infection
  - Skin erosion above the alfapump
  - Wound dehiscence
  - Pain

- Surgical
  - Wound dehiscence (rupture)
  - Ascitic fluid leakage
  - Bladder perforation
  - Seroma

- Catheters
  - Kinking
  - Clogging
  - Disconnection from pump
  - Dislocation

- Migration
- Infection
- Tissue damage over catheter trajectory (including erosion)

- alfapump®
  - Erosion
  - Dysfunction
  - Device migration
  - Discomfort during pumping (sensation over the abdomen, filling of the bladder)
  - Externally mediated damage (trauma, radiation)
  - Clogging (prolonged shake mode)

- Infection
  - Peritonitis (abdominal inflammation)
  - Pump pocket
  - Skin
  - Sepsis (including septic shock)
  - Urinary tract
  - Pneumonia
  - Surgical incision

- Reduced kidney function
  - Electrolyte disturbance
  - Acute kidney injury
  - Hepatorenal syndrome
  - Kidney failure

- Genito-urinary complications
  - Hematuria
  - Urethral stenosis
  - Bladder injury
  - Urinary retention
  - Incontinence/leakage
  - Bladder irritation/spasm
    -

- Hepatic encephalopathy
  - Mild-grade I or II
  - Severe-grade III or IV

- Hepatic
  - Progression of liver disease

- Systemic effects
  - Protein loss (hypoalbuminemia)

- Circulatory dysfunction (similar to post paracentesis circulatory dysfunction)
- Dehydration
- Death

The above risks may require intervention to address the condition.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

A.1 Performance and Safety Testing

Testing to verify that the alfapump® System functions as intended, and all system level design and functional specifications are met.

A.1.1 alfapump®

Testing was conducted on the alfapump® model AFS50.3, including: mechanical design verification, electrical and firmware design verification testing and electromagnetic compatibility testing. Key testing on the alfapump® is summarized in

Table 1. Testing demonstrated the alfapump® operated according to specifications after exposure to the tested conditions (i.e., passed testing). In addition, testing and evaluation was performed to verify that the applicable components of the alfapump® System meets its requirement to comply with International Standards Organization (ISO) 14708-1:2014 which specifies requirements that are applicable to active implantable medical devices (AIMD).

Table 1 alfapump® Performance and Safety Testing

Test	Purpose	Acceptance Criteria	Results
Output volume and flow rate	To verify the flowrate and the output volume of alfapump®.	The alfapump® flow rate and output volume are within the specified criteria.	Passed
Long time tests / Maximum Daily Volume	To verify the maximum cumulative volume of Ascitic Fluid transport by the alfapump®.	The actual aspirated volume and the volume calculated from the alfapump® are within specified criteria when pumping for 1 hour and the daily volume transport is set to 4 L/per day.	Passed
Dimensional Requirements	To demonstrate that alfapump® meet shape and profile requirements.	Alfapump® samples must meet size specifications for IPG width, height, thickness, volume, mass, and radius.	Passed
Environmental Conditions / Vibration Test	To demonstrate that alfapump® is able to withstand the mechanical forces which might occur during normal conditions of use, including the time prior to implant.	Testing per ISO 14708-1:2014 clause 23.2.	Passed
Environmental Conditions / Shock Test	To demonstrate that alfapump® is constructed so that minor mechanical shocks caused by mishandling during the implant procedure do not damage the implantable parts of the active implantable medical device.	Testing per ISO 14708-1:2014 clause 23.7.	Passed
Environmental Conditions / Pressure Test	To demonstrate that alfapump® is constructed to withstand the changes of pressure which can occur during transit or normal conditions of use.	Testing per ISO 14708-1:2014 clause 25.	Passed
Protection from excessive temperature	To demonstrate that no outer surface of the alfapump® is greater than 2 °C above the normal surrounding body temperature of 37 °C when implanted, and when the active implantable medical device is in normal operation or in any single component failure.	The surface temperature of the alfapump® implant does not exceed 39°C when implanted, when the implant is operating in a normal condition and when the implant is working in any single-fault condition.	Passed

Table 2 alfapump® Performance and Safety Testing continued

Test	Purpose	Acceptance Criteria	Results
Ultrasound testing	To demonstrate that alfapump® is designed and constructed so that no irreversible change will be caused by exposure to diagnostic levels of ultrasonic energy.	Testing per ISO 14708-1:2014 clause 22.1.	Passed
Catheters Interface and Pull-Force	The purpose of this test is to measure the force required to disconnect the catheters from the alfapump®.	Disconnection force >= 10N for Bladder Catheter and Peritoneal Catheter Extension.	Passed
Minimum Peritoneal Pressure	To verify that there is no fluid transport if the peritoneal pressure is below the Minimum Peritoneal Cavity Pressure (minPP).	When the peritoneal pressure is below minPP the fluid transport is suspended.	Passed
Maximum Bladder Pressure	To verify that there is no fluid transport if the bladder pressure exceeds the Maximum Bladder Pressure (maxBP) relative to the pressure in the peritoneal cavity.	When the bladder pressure is above maxBP the fluid transport is suspended.	Passed
Battery	The purpose of this test is to verify the battery used in the alfapump®: Electrical, Visual, Dimensional, Crush, Continuous Charge, External Short Circuit, Free Fall, Thermal Abuse, Forced Discharge and Temperature Abuse.	Testing per International Electrotechnical Commission (IEC) 62133-2:2017/Amd1:2021.	Passed
Battery Capacity	To verify alfapump® battery capacity.	The alfapump® shall be able to pump 1 liter per day for at least 4 consecutive days without getting charged when the battery is new and fully charged.	Passed

A.1.2 Smart Charger and Docking Station

Testing was conducted on the Smart Charger model P5 and on the Docking Station, including: mechanical design verification, electrical and firmware design verification testing. Key testing on the Smart Charger model P5 and on the Docking Station is summarized in

Table 3. Testing demonstrated the alfapump® operated according to specifications after exposure to the tested conditions (i.e., passed testing).

Table 3 Smart Charger and Docking Station performance and safety testing

Test	Purpose	Acceptance Criteria	Results
Programming Wireless Radio Frequency	To verify that the radio frequencies communication function perform as intended.	The wireless radio communication between the Smart Charger and the alfapump® is based on a single channel communication at a frequency of 907±1 MHz.	Passed
Charge test	To verify that through a simulated battery the charging current is between adequate values.	Charging current in the range of 0.8 - 4A (0.2 - 1C of the 4000 mAh battery).	Passed
DC Leakage Current	To demonstrate that the leakage currents are within an acceptable range.	Testing per IEC 60601-1:2005/Amd2:2020 clause 8.	Passed
Mechanical resistance	To demonstrate that the Smart Charger and the Docking Station are able to withstand external mechanical forces.	Testing per IEC 60601-1:2005/Amd2:2020 clauses 9 and 15.	Passed
Protection from excessive temperature	To demonstrate that the Smart Charger and the Docking Station do not cause any temperature-related harm to the patient.	Testing per IEC 60601-1:2005/Amd2:2020 clause 11.	Passed
Battery Protection	To verify that the charge FET switches off with over voltage, charge FET switches off with under voltage and FET switches off with over current.	Over-voltage, under-voltage, over-currents are tested and safety is ensured.	Passed
Battery	The purpose of this test is to verify the battery used in the Smart Charger: Electrical, Visual, Dimensional, Crush, Continuous Charge, External Short Circuit, Free Fall, Thermal Abuse, Forced Discharge and Temperature Abuse.	Testing per IEC 62133-2:2017/Amd1:2021.	Passed

A.1.3 Bladder Catheter and Peritoneal Catheter SNCA-5262L

Mechanical design verification testing was conducted on the Bladder Catheter and Peritoneal Catheter SNCA-5262L used in conjunction with alfapump® model AFS50.3. Key testing on the Bladder Catheter and the Peritoneal Catheter SNCA-5262L is summarized in

Table 4. Testing demonstrated the Bladder Catheter and the Peritoneal Catheter SNCA-5262L operated according to specifications after exposure to the tested conditions (i.e., passed testing).

Table 4 Bladder Catheter and Peritoneal Catheter SNCA-5262L performance and safety testing

Test	Purpose	Acceptance Criteria	Results
Dimensional Requirements	To demonstrate that catheters meet shape and profile requirements.	Bladder Catheter and Peritoneal Catheter SNCA-5262L samples must meet size specifications for IPG width, height, thickness, volume, mass, and radius.	Passed.
Connector Pull Force	To verify that the Bladder Catheter does not disconnect from the connector under a defined load.	After applying 5 N for 60 seconds and 10 N for 10 seconds, the Bladder Catheter is still attached to the connector.	Passed.
Leakage Specification	To verify that the bladder catheter can withstand a fluid pressure of 2 bar for 20 seconds.	The bladder catheter does not burst or have any visible leaks when a fluid pressure of 2 bar is applied for 20 seconds.	Passed.
Kink Resistance	To verify that no kinking or flow obstruction occurs when the Bladder Catheter is bent over 180°.	The Bladder Catheter does not kink or get obstructed, when it is bent over 180° on a 25 mm diameter circle. (Minimum of 150 mL transported in 60s when attached to a 100 cm water column).	Passed.
alfapump Pull Force	To verify that the Bladder Catheter does not get disconnected from the nipple of the alfapump® when an axial force is applied on the Bladder Catheter.	The Bladder Catheter does not disconnect from the nipple of the alfapump® when a tensile force of 5 N for 60 s and 10 N for 10 s is applied on the Bladder Catheter.	Passed.
Tunneling Rod Pull Force	To verify that the Bladder Catheter does not get disconnected from the Tunneling Rod when an axial force is applied on the Bladder Catheter.	The Bladder Catheter does not disconnect from the Tunneling Rod when a tensile force of 5 N for 60 s and 10 N for 10 s is applied on the Bladder Catheter.	Passed.
Connector Pull Force	To demonstrate, that the Peritoneal Catheter SNCA-5262L does not disconnect from the catheter connector when a tensile force is applied on the Peritoneal Catheter SNCA-5262L.	After applying 5N for 60 seconds and 10 N for 10 seconds, the Peritoneal Catheter SNCA-5262L is still attached at the connector.	Passed.
Leakage Specification	To verify, that no leakage or burst occurs, when applying 2 bar for 20 seconds onto a fluid filled Peritoneal Catheter SNCA-5262L.	No burst or leakage occurs when applying 2 bar for 20 seconds to a fluid filled Peritoneal Catheter SNCA-5262L .	Passed.
Kink Resistance	To verify that Peritoneal Catheter SNCA-5262L does not kink, when it is bent over 180°.	The Peritoneal Catheter SNCA-5262L does not kink or get obstructed, when it is bent over 180° on a 25 mm diameter circle.	Passed.

A.1.3 alfapump® System testing

Testing to verify that system-level design requirements were met for interactions between alfapump® System components was performed. All test articles met defined acceptance criteria for the system integration tests conducted. System validation testing demonstrated that the system operated as expected and has been validated for safe and effective use.

A.2 Human Factors Testing

Sequana Medical executed a comprehensive human factors and usability engineering process that followed and complied with the FDA-recognized standards IEC 62366-1:2015+AMDI:2020 and ANSI/AAMI HE75:2009 as well as the FDA's guidance document, Applying Human Factors and Usability Engineering to Medical Devices" (February 3, 2016). **Table 5** summarizes summative usability evaluations performed to demonstrate safe and effective use of the alfapump® System with intended users in the expected use environments, including associated training (as applicable) and accompanying documentation.

Table 5 Human Factors testing

Test	Purpose	Acceptance Criteria	Results
alfapump® System(Implantation) Summative Usability Testing	To evaluate the usability of implantation process of an alfapump® System by the IR and to evaluate the outcomes.	The usability evaluation can be considered passed if no acceptable risks arise from the identified use events.	Passed.
FlowTech Software Summative Usability Testing	Main objective was to evaluate the usability of the FlowTech Software by trained physicians, field staff, patients, and unsterile assistants.	The usability evaluation can be considered passed if no acceptable risks arise from the identified use events.	Passed.
FlowControl Software Summative Usability Testing	Main objective was to determine the safety and effectiveness of the FlowControl Software by trained physicians, field staff, patients and unsterile assistants.	The usability evaluation can be considered passed if no acceptable risks arise from the identified use events.	Passed.
Smart Charger Summative Usability Testing	Main objective was to determine the safety and effectiveness of the Smart Charger by implant physicians, following physicians, field staff (Clinical Specialists) and patients.	The usability evaluation can be considered passed if no acceptable risks arise from the identified use events.	Passed.

A.3 Sterilization Validation

The alfapump® System sterile components are ethylene oxide sterilized per the requirements of ISO 11135:2014_A1:2018, "Medical devices-Validation and routine control of ethylene oxide sterilization," The validation results demonstrated that the sterilization process achieves a minimum sterility assurance level (SAL) of 10^{-6} and that residual levels were within the acceptable ranges for an implant according to ISO 10993-7, "Biological evaluation of medical devices --Part7: Ethylene oxide sterilization residuals."

Table 6 summarizes testing per ISO 11135:2014/A1:2018 for sterilization validation of applicable components alfapump® System with acceptable results.

Table 6 Sterilization Validation

Test	Purpose	Acceptance Criteria	Results
Product bioburden	The contamination of the product families was checked by performing bioburden analysis on 3 test units selected randomly for each of the following products: alfapump®, Bladder Catheter, Peritoneal Catheter SNCA-5262L, Introducer Kit and Implant Accessories. Prior to routine testing, validation of the method was performed according to ISO 11737-1 to determine the adequacy of the laboratory technique to recover the micro-organisms inoculated on the following products: alfapump®, Bladder Catheter, Peritoneal Catheter SNCA-5262L, Introducer Kit and Implant Accessories.	• The corrected bioburden shall not exceed Alert Limit 50 CFU/product and Action Limit 100 CFU / product. • Bioburden suitability: the recovery efficiency for the bioburden validation shall be ≥ 50%. Correction factor shall be <2%. The products shall be not inhibitory min 50%	Passed.
Test of product sterility	A sterility test on 3 samples of alfapump®, Bladder Catheter, Tunneling Rod, Peritoneal Catheter SNCA-5262L, Introducer Kits and Implant Accessories was done after one short cycle run to prove that the Positive Control Devices (PCDs) are more resistant than product bioburden. Validation of the sterility test method was performed according 11737-2 on all 6 products: alfapump®, Bladder Catheter, Tunneling Rod, Peritoneal Catheter SNCA-5262L, Introducer Kits and Implant Accessories.	• A sterility test following a sub-lethal cycle shall show no growth observed in all product samples. • Validation of the sterility test method (Bacteriostasis / fungistasis) of each product test shall show no antimicrobial or antifungal activity.	Passed.
Bacterial endotoxin test (LAL)	Evaluation of the endotoxin concentration of the selected worst-cases products was determined on 3 samples of alfapump®, Bladder Catheter, Tunneling Rod, Peritoneal Catheter SCNA-526L, Introducer Kit	• Bacterial endotoxin test shall show bacterial endotoxin level <20 EU/device. • Validation of the LAL test method was performed on each product to determine the Maximum Valid Dilution (MVD).	Passed.

Test	Purpose	Acceptance Criteria	Results
	and Implant Accessories each selected from three production lots.		
EO + ECH residual testing (following each of the two full sterilization cycles) for limited contact device (<24h).	The aim of the ethylene oxide (EO)/ethylene chlorohydrin (ECH) residual testing is to find the aeration time at the end of routine sterilization cycle. This aeration time (hot degassing in the aeration cell and / or ambient aeration) shall ensure that the levels of EO/ECH residuals pose a minimal risk to the patient in normal product use. This testing was performed for Introducer Kit and Tunneling rod.	• EtO: o 4 mg / day o TCL: 10 µg/cm2 • ECH: o 9 mg / day o TCL: 5 mg/cm2	Passed.
EO + ECH residual testing (following each of the two full sterilization cycles) for Long-term contact devices (>30d).	The aim of the EO/ECH residual testing is to find the aeration time at the end of routine sterilization cycle. This aeration time (hot degassing in the aeration cell and / or ambient aeration) shall ensure that the levels of EO/ECH residuals pose a minimal risk to the patient in normal product use. This testing was performed for alfapump®, Bladder Catheter, Peritoneal Catheter SCNA-526L and Implant Accessories	• EtO: o 2.5 g / lifetime o 60 mg / first 30 days o 4 mg / first 24 hours o 0.1 mg / day o TCL: 10 µg/cm2 • ECH: o 10 g / lifetime o 60 mg / first 30 days o 9 mg / first 24 hours o 0.4 mg / day TCL: 5 mg/cm2	Passed.
Short Cycle	The resistance of PCDs compared to product bioburden should be demonstrated. The resistance of Enhanced Positive Control Devices (EPCDs) should be shown to be equal or greater than the resistance of Internal Positive Control Devices (IPCDs). The following products were tested regarding sterility on 6 samples each: alfapump®, Bladder Catheter, Tunneling Rod, Peritoneal	• Positive BIs should be found to determine the adequacy of laboratory technique • All the positive growths should be true positives • Resistance of EPCDs ≥ resistance of IPCDs • All products must be sterile	Passed

Test	Purpose	Acceptance Criteria	Results
	Catheter SCNA-526L, Introducer Kit and Implant Accessories		
Half Cycle	A total of three consecutive half cycles in the same Sterox chamber resulting in total inactivation of the biological indicators (with a population not less than 106) were performed to confirm the minimum exposure time. The specified exposure time shall be at least double this minimum time.	• All biological indicators (BIs) should be negative	Passed

A.4 Biocompatibility

Biocompatibility testing was conducted in accordance with ISO 10993-1:2018 and FDA guidance document Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process" (September 8, 2023).

Table 7 summarizes testing conducted to support the biological safety of the alfapump® System (alfapump®, Bladder Catheter, Peritoneal Catheter SNCA-5262L, Implant Accessories, Introducer Kit, Tunneling Rod, Smart Charger, and Docking Station).

Table 7 Biocompatibility testing

Test	Purpose	Acceptance Criteria	Results
alfapump			
Cytotoxicity	The purpose of this Good Laboratory Practices (GLP) study was to evaluate the potential cytotoxic effect of a test article extract using an in vitro mammalian cell culture. This study was conducted according to the ISO 10993-5:2009.	The full strength EMEM10 test article extract shall show no cytotoxic potential to L-929 mouse fibroblast cells. alfapump shall be non-cytotoxic.	Passed.
Irritation	The purpose of this non-clinical GLP study was to evaluate the potential of test article extracts to induce local dermal irritation following intracutaneous injection in rabbits. This study was conducted according to the ISO 10993-23:2021.	The difference between each test extract overall mean score and corresponding control blank overall mean score shall be lower than 1.0 (0.0 for the SC and SO test extracts). alfapump shall be non-irritating.	Passed.
Sensitization	The purpose of this non-clinical GLP study was to evaluate the potential of the test article extracts to cause delayed dermal contact sensitization in the guinea pig. This study was conducted according to the ISO 10993-10:2021.	The topical application of the SC extract shall not induce delayed sensitization in the guinea pig. The topical application of the SO extract shall not induce delayed sensitization in the guinea pig. alfapump shall be non-sensitizing.	Passed.
Pyrogenicity (EP)	The purpose of this non-clinical GLP	alfapump shall be non-pyrogenic.	Passed.

Test	Purpose	Acceptance Criteria	Results
	study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the European Pharmacopoeia.		
Pyrogenicity (USP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the United States Pharmacopoeia, General chapter <151>.	alfapump shall be non-pyrogenic.	Passed.
Acute systemic toxicity	The purpose of this non-clinical GLP study was to evaluate the acute systemic toxicity of the sodium chloride (SC) test article extract following intravenous (IV) and intraperitoneal (IP) injection in mice. This study was conducted according to ISO 10993-11:2017	There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IV route. There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IP route.	Passed.

Test	Purpose	Acceptance Criteria	Results
Genotoxicity endpoint (Bacterial Reverse Mutation)	Bacterial reverse mutation tests have been used for the determination of mutagenic and potential carcinogenic hazards of the alfapump®. This study was conducted according to ISO 10993-3:2014. This study was also conducted according to the Organization for Economic Cooperation and Development (OECD) 471 (2020), Guideline for Testing of Chemicals, Bacterial Reverse Mutation Test.	The SC and DMSO test article extracts shall be considered to be non-mutagenic to S. typhimurium tester strains TA98, TAl00, TA1535, and TA1537, and to E. coli WP2uvrA tester strain. The test article shall be not mutagenic.	Passed.
Genotoxicity (In Vitro Mouse Lymphoma Assay)	The purpose of this non-clinical GLP study was to evaluate the mutagenic potential of the test article extracts using the mouse lymphoma forward mutation assay procedures utilizing 4 hours treatments in the absence and presence of exogenous metabolic activation and 24 hours treatment (in the absence of exogenous metabolic activation). This study was conducted according to ISO 10993-3:2014. This study was also	The $RPMI_0$ and DMSO test article extracts shall not cause any increase in the mean mutant frequency of the L5178Y/$TK^{+/-}$ cell line greater than the mutant frequency of the control blank + the Global Evaluation Factor (126), in the presence or absence of metabolic activation. The test article shall be not mutagenic.	Passed.

Test	Purpose	Acceptance Criteria	Results
	conducted according to the Organization for Economic Cooperation and Development (OECD) 490 (2016), Guideline for Testing of Chemicals, In Vitro Mammalian Cell Gene Mutation Tests using the Thymidine Kinase Gene.		

Test	Purpose	Acceptance Criteria	Results
4 weeks and 13 weeks Implantation Study	The purpose of this nonclinical GLP study was to evaluate the local tissue effects of an ingrowth patch and two implant accessories belonging to the alfapump® System. The ingrowth patch (Test Article 1) was compared to a CE-marked ingrowth patch (Control Article) and to a negative control (High Density PolyEthylene, HDPE) and the peritoneal catheter extension (Test Article 2) and catheter extension connector (Test Article 3) were compared to the negative control article only following subcutaneous implantation in the rabbit. The local tissue effects were evaluated macroscopically and histopathologically 4 and 13 weeks post-implantation. This study was conducted according to ISO 10993-6:2016.	Null to minimal reaction when compared to control or the negative control article.	Passed.

Test	Purpose	Acceptance Criteria	Results
Chemical characterization	The purpose of this study was to perform a chemical characterization to identify and quantitate the extractables and/or leachables that may be released from the test article. This study was conducted according to ISO 10993-18:2020 / Amd1:2022.	Identify and quantitate the extractables and/or leachables that may be released from the test article	Passed.
Compound and element analysis of alfapump after exhaustive extraction using ICP-MS/-OES	The purpose of this study was to perform a Compound and element analysis after exhaustive extraction (ICP-MS/-OES) to identify and quantify the extractables and/or leachables that may be released from the test article. This study was conducted based on guidance provided in ISO 10993-18:2020 / Amd1:2022.	Identify and quantify the extractables and/or leachables that may be released from the test article (alfapump®).	Passed.
Peritoneal Catheter SNCA-5262L			
Cytotoxicity	The purpose of this GLP study was to evaluate the potential cytotoxic effect of a test article extract using an in vitro mammalian cell culture. This study was conducted according to the ISO 10993-5:2009.	The full strength EMEM10 test article extract shall show no cytotoxic potential to L-929 mouse fibroblast cells. Peritoneal Catheter SNCA-5262L shall be non-cytotoxic.	Passed.

Test	Purpose	Acceptance Criteria	Results
Irritation	The purpose of this non-clinical GLP study was to evaluate the potential of test article extracts to induce local dermal irritation following intracutaneous injection in rabbits. This study was conducted according to the ISO 10993-23:2021.	The difference between each test extract overall mean score and corresponding control blank overall mean score shall be lower than 1.0 (0.0 for the SC and SO test extracts). Peritoneal Catheter SNCA-5262L shall be non-irritating.	Passed.
Sensitization	The purpose of this non-clinical GLP study was to evaluate the potential of the test article extracts to cause delayed dermal contact sensitization in the guinea pig. This study was conducted according to the ISO 10993-10:2021.	The topical application of the SC extract shall not induce delayed sensitization in the guinea pig. The topical application of the SO extract shall not induce delayed sensitization in the guinea pig. Peritoneal Catheter SNCA-5262L shall be non-sensitizing.	Passed.

Test	Purpose	Acceptance Criteria	Results
Pyrogenicity (USP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the United States Pharmacopoeia, General chapter <151>.	Peritoneal Catheter SNCA-5262L shall be non-pyrogenic.	Passed.
Acute systemic toxicity	The purpose of this non-clinical GLP study was to evaluate the acute systemic toxicity of the sodium chloride (SC) test article extract following intravenous (IV) and intraperitoneal (IP) injection in mice. This study was conducted according to ISO 10993-11:2017	There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IV route. There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IP route.	Passed.
Genotoxicity (Bacterial Reverse Mutation Study)	Bacterial reverse mutation tests have been used for the determination of mutagenic and potential carcinogenic hazards of the Peritoneal Catheter SNCA-5262L. This study was conducted according to ISO 10993-3:2014. This study was also	The SC and DMSO test article extracts shall be considered to be non-mutagenic to S. typhimurium tester strains TA98, TAl00, TA1535, and TA1537, and to E. coli WP2uvrA tester strain.	Passed.

Test	Purpose	Acceptance Criteria	Results
	conducted according to the Organization for Economic Cooperation and Development (OECD) 471 (2020), Guideline for Testing of Chemicals, Bacterial Reverse Mutation Test.	The test article shall be not mutagenic.	

Test	Purpose	Acceptance Criteria	Results
Genotoxicity (In Vitro Mouse Lymphoma Assay)	The purpose of this non-clinical GLP study was to evaluate the mutagenic potential of the test article extracts using the mouse lymphoma forward mutation assay procedures utilizing 4 hours treatments in the absence and presence of exogenous metabolic activation and 24 hours treatment (in the absence of exogenous metabolic activation). This study was conducted according to ISO 10993-3:2014. This study was also conducted according to the Organization for Economic Cooperation and Development (OECD) 490 (2016), Guideline for Testing of Chemicals, In Vitro Mammalian Cell Gene Mutation Tests using the Thymidine Kinase Gene.	The $RPMI_0$ and DMSO test article extracts shall not cause any increase in the mean mutant frequency of the $L5178Y/TK^{+/-}$ cell line greater than the mutant frequency of the control blank + the Global Evaluation Factor (126), in the presence or absence of metabolic activation. The test article shall be not mutagenic.	Passed.

Test	Purpose	Acceptance Criteria	Results
Chemical characterization	The purpose of this study was to perform a chemical characterization to identify and quantitate the extractables and/or leachables that may be released from the test article. This study was conducted according to ISO 10993-18:2020 / Amd1:2022.	Identify and quantitate the extractables and/or leachables that may be released from the test article (Peritoneal Catheter SNCA-5262L).	Passed.
Bladder Catheter			
Cytotoxicity	The purpose of this GLP study was to evaluate the potential cytotoxic effect of a test article extract using an in vitro mammalian cell culture. This study was conducted according to the ISO 10993-5:2009.	The full strength EMEM10 test article extract shall show no cytotoxic potential to L-929 mouse fibroblast cells. Bladder Catheter shall be non-cytotoxic.	Passed.
Pyrogenicity (EP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the European Pharmacopoeia.	Bladder Catheter shall be non-pyrogenic.	Passed.

Test	Purpose	Acceptance Criteria	Results
Pyrogenicity (USP) e	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the United States Pharmacopoeia, General chapter <151>.	Bladder Catheter shall be non-pyrogenic.	Passed.
Chemical characterization	The purpose of this study was to perform a chemical characterization to identify and quantitate the extractables and/or leachables that may be released from the test article. This study was conducted according to ISO 10993-18:2020 / Amd1:2022.	Identify and quantitate the extractables and/or leachables that may be released from the test article (Bladder Catheter).	Passed.
Implant Accessories			
Peritoneal Catheter Extension			
Cytotoxicity	The purpose of this GLP study was to evaluate the potential cytotoxic effect of a test article extract using an in vitro mammalian cell culture. This study was conducted according to the ISO 10993-5:2009.	The full strength EMEM10 test article extract shall show no cytotoxic potential to L-929 mouse fibroblast cells. Peritoneal Catheter Extension shall be non-cytotoxic.	Passed.

Test	Purpose	Acceptance Criteria	Results
Irritation	The purpose of this non-clinical GLP study was to evaluate the potential of test article extracts to induce local dermal irritation following intracutaneous injection in rabbits. This study was conducted according to the ISO 10993-23:2021.	The difference between each test extract overall mean score and corresponding control blank overall mean score shall be lower than 1.0 (0.0 for the SC and SO test extracts). Peritoneal Catheter Extension shall be non-irritating.	Passed.
Sensitization	The purpose of this non-clinical GLP study was to evaluate the potential of the test article extracts to cause delayed dermal contact sensitization in the guinea pig. This study was conducted according to the ISO 10993-10:2021.	The topical application of the SC extract shall not induce delayed sensitization in the guinea pig. The topical application of the SO extract shall not induce delayed sensitization in the guinea pig. Peritoneal Catheter Extension shall be non-sensitizing.	Passed.
Pyrogenicity (EP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the European Pharmacopoeia.	Peritoneal Catheter Extension shall be non-pyrogenic.	Passed.
Pyrogenicity (USP)	The purpose of this non-clinical GLP study was to evaluate	Peritoneal Catheter Extension shall be non-pyrogenic.	Passed.

Test	Purpose	Acceptance Criteria	Results
	if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the United States Pharmacopoeia, General chapter <151>.		

Test	Purpose	Acceptance Criteria	Results
Acute systemic toxicity	The purpose of this non-clinical GLP study was to evaluate the acute systemic toxicity of the sodium chloride (SC) test article extract following intravenous (IV) and intraperitoneal (IP) injection in mice. This study was conducted according to ISO 10993-11:2017	There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IV route. There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IP route.	Passed.
Genotoxicity (Bacterial Reverse Mutation)	Bacterial reverse mutation tests have been used for the determination of mutagenic and potential carcinogenic hazards of the Peritoneal Catheter Extension. This study was conducted according to ISO 10993-3:2014. This study was also conducted according to the Organization for Economic Cooperation and Development (OECD) 471 (2020), Guideline for Testing of Chemicals, Bacterial Reverse Mutation Test.	The SC and DMSO test article extracts shall be considered to be non-mutagenic to S. typhimurium tester strains TA98, TAl00, TA1535, and TA1537, and to E. coli WP2uvrA tester strain. The test article shall be not mutagenic.	Passed.

Test	Purpose	Acceptance Criteria	Results
Genotoxicity (In Vitro Mouse Lymphoma Assay	The purpose of this non-clinical GLP study was to evaluate the mutagenic potential of the test article extracts using the mouse lymphoma forward mutation assay procedures utilizing 4 hours treatments in the absence and presence of exogenous metabolic activation and 24 hours treatment (in the absence of exogenous metabolic activation). This study was conducted according to ISO 10993-3:2014. This study was also conducted according to the Organization for Economic Cooperation and Development (OECD) 490 (2016), Guideline for Testing of Chemicals, In Vitro Mammalian Cell Gene Mutation Tests using the Thymidine Kinase Gene.	The $RPMI_0$ and DMSO test article extracts shall not cause any increase in the mean mutant frequency of the $L5178Y/TK^{+/-}$ cell line greater than the mutant frequency of the control blank + the Global Evaluation Factor (126), in the presence or absence of metabolic activation. The test article shall be not mutagenic.	Passed.

Test	Purpose	Acceptance Criteria	Results
Chemical characterization	The purpose of this study was to perform a chemical characterization to identify and quantitate the extractables and/or leachables that may be released from the test article. This study was conducted according to ISO 10993-18:2020 / Amd1:2022.	Identify and quantitate the extractables and/or leachables that may be released from the test article (Peritoneal Catheter Extension).	Passed.
Catheter Extension Connector			
Cytotoxicity	The purpose of this GLP study was to evaluate the potential cytotoxic effect of a test article extract using an in vitro mammalian cell culture. This study was conducted according to the ISO 10993-5:2009.	The full strength EMEM10 test article extract shall show no cytotoxic potential to L-929 mouse fibroblast cells. Catheter Extension Connector shall be non-cytotoxic.	Passed.
Irritation	The purpose of this non-clinical GLP study was to evaluate the potential of test article extracts to induce local dermal irritation following intracutaneous injection in rabbits. This study was conducted according to the ISO 10993-23:2021.	The difference between each test extract overall mean score and corresponding control blank overall mean score shall be lower than 1.0 (0.0 for the SC and SO test extracts). Catheter Extension Connector shall be non-irritating.	Passed.
Sensitization	The purpose of this non-clinical GLP study was to evaluate	The topical application of the SC extract shall not	Passed.

Test	Purpose	Acceptance Criteria	Results
	the potential of the test article extracts to cause delayed dermal contact sensitization in the guinea pig. This study was conducted according to the ISO 10993-10:2021.	induce delayed sensitization in the guinea pig. The topical application of the SO extract shall not induce delayed sensitization in the guinea pig. Catheter Extension Connector shall be non-sensitizing.	
Pyrogenicity (EP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the European Pharmacopoeia.	Catheter Extension Connector shall be non-pyrogenic.	Passed.
Pyrogenicity (USP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the United States Pharmacopoeia, General chapter <151>.	Catheter Extension Connector shall be non-pyrogenic.	Passed.
Chemical characterization	The purpose of this study was to perform a chemical characterization to	Identify and quantitate the extractables and/or leachables that may	Passed.

Test	Purpose	Acceptance Criteria	Results
	identify and quantitate the extractables and/or leachables that may be released from the test article. This study was conducted according to ISO 10993-18:2020 / Amd1:2022.	be released from the test article (Catheter Extension Connector).	
Implantation study Peritoneal Catheter Extension & Catheter Extension Connector	The purpose of this nonclinical GLP study was to evaluate the local tissue effects of an ingrowth patch and two implant accessories belonging to the alfapump® System. The ingrowth patch (Test Article 1) was compared to a CE-marketed ingrowth patch (Control Article) and to a negative control (High Density PolyEthylene, HDPE) and the Peritoneal Catheter Extension (Test Article 2) and Catheter Extension Connector (Test Article 3) were compared to the negative control article only following subcutaneous implantation in the rabbit. The local tissue effects were evaluated macroscopically and histopathologically 4 and 13 weeks post-	Null to minimal reaction when compared to control or the negative control article.	Passed.

Test	Purpose	Acceptance Criteria	Results
	implantation. This study was conducted according to ISO 10993-6:2016.		
Introducer Kit (0.038 Double-Ended Guidewire)			
Cytotoxicity(0.038 Double-Ended Guidewire)	The purpose of this GLP study was to evaluate the potential cytotoxic effect of a test article extract using an in vitro mammalian cell culture. This study was conducted according to the ISO 10993-5:2009.	The full strength EMEM10 test article extract shall show no cytotoxic potential to L-929 mouse fibroblast cells. 0.038 Double-Ended Guidewire shall be non-cytotoxic.	Passed.
Irritation	The purpose of this non-clinical GLP study was to evaluate the potential of test article extracts to induce local dermal irritation following intracutaneous injection in rabbits. This study was conducted according to the ISO 10993-23:2021.	The difference between each test extract overall mean score and corresponding control blank overall mean score shall be lower than 1.0 (0.0 for the SC and SO test extracts). 0.038 Double-Ended Guidewire shall be non-irritating.	Passed.
Sensitization	The purpose of this non-clinical GLP study was to evaluate the potential of the test article extracts to cause delayed dermal contact sensitization in the guinea pig. This study was conducted according	The topical application of the SC extract shall not induce delayed sensitization in the guinea pig. The topical application of the SO extract shall not induce delayed sensitization in the guinea pig. 0.038 Double-Ended	Passed.

Test	Purpose	Acceptance Criteria	Results
	to the ISO 10993-10:2021.	Guidewire shall be non-sensitizing.	
Pyrogenicity (EP) (0.038 Double-Ended Guidewire)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the European Pharmacopoeia.	0.038 Double-Ended Guidewire shall be non-pyrogenic.	Passed.
Pyrogenicity (USP) (0.038 Double-Ended Guidewire)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the United States Pharmacopoeia, General chapter <151>.	0.038 Double-Ended Guidewire shall be non-pyrogenic.	Passed.
Acute systemic toxicity (0.038 Double-Ended Guidewire)	The purpose of this non-clinical GLP study was to evaluate the acute systemic toxicity of the sodium chloride (SC) test article extract following intravenous (IV) and intraperitoneal (IP) injection in mice. This study was	There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IV route. There shall be no mortality or evidence of systemic toxicity	Passed.

Test	Purpose	Acceptance Criteria	Results
	conducted according to ISO 10993-11:2017	from the SC test article extract injected into mice by the IP route.	
14 FR Dilator			
Cytotoxicity	The purpose of this GLP study was to evaluate the potential cytotoxic effect of a test article extract using an in vitro mammalian cell culture. This study was conducted according to the ISO 10993-5:2009.	The full strength EMEM10 test article extract shall show no cytotoxic potential to L-929 mouse fibroblast cells. 14 FR Dilator shall be non-cytotoxic.	Passed.
Irritation	The purpose of this non-clinical GLP study was to evaluate the potential of test article extracts to induce local dermal irritation following intracutaneous injection in rabbits. This study was conducted according to the ISO 10993-23:2021.	The difference between each test extract overall mean score and corresponding control blank overall mean score shall be lower than 1.0 (0.0 for the SC and SO test extracts). 14 FR Dilator shall be non-irritating.	Passed.
Sensitization	The purpose of this non-clinical GLP study was to evaluate the potential of the test article extracts to cause delayed dermal contact sensitization in the guinea pig. This study was conducted according to the ISO 10993-10:2021.	The topical application of the SC extract shall not induce delayed sensitization in the guinea pig. The topical application of the SO extract shall not induce delayed sensitization in the guinea pig. 14 Fr Dilator shall be non-sensitizing.	Passed.

Test	Purpose	Acceptance Criteria	Results
Pyrogenicity (EP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the European Pharmacopoeia.	14 Fr Dilator shall be non-pyrogenic.	Passed.
Pyrogenicity (USP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the United States Pharmacopoeia, General chapter <151>.	14 Fr Dilator shall be non-pyrogenic.	Passed.
Acute systemic toxicity	The purpose of this non-clinical GLP study was to evaluate the acute systemic toxicity of the sodium chloride (SC) test article extract following intravenous (IV) and intraperitoneal (IP) injection in mice. This study was conducted according to ISO 10993-11:2017	There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IV route. There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IP route.	Passed.

Test	Purpose	Acceptance Criteria	Results
18 Fr Peel-Away Introducer Sheath			
Cytotoxicity	The purpose of this GLP study was to evaluate the potential cytotoxic effect of a test article extract using an in vitro mammalian cell culture. This study was conducted according to the ISO 10993-5:2009.	The full strength EMEM10 test article extract shall show no cytotoxic potential to L-929 mouse fibroblast cells. 18 Fr Peel-Away Introducer Sheath shall be non-cytotoxic.	Passed.
Irritation	The purpose of this non-clinical GLP study was to evaluate the potential of test article extracts to induce local dermal irritation following intracutaneous injection in rabbits. This study was conducted according to the ISO 10993-23:2021.	The difference between each test extract overall mean score and corresponding control blank overall mean score shall be lower than 1.0 (0.0 for the SC and SO test extracts). 18 Fr Peel-Away Introducer Sheath shall be non-irritating.	Passed.
Sensitization	The purpose of this non-clinical GLP study was to evaluate the potential of the test article extracts to cause delayed dermal contact sensitization in the guinea pig. This study was conducted according to the ISO 10993-10:2021.	The topical application of the SC extract shall not induce delayed sensitization in the guinea pig. The topical application of the SO extract shall not induce delayed sensitization in the guinea pig. 18 Fr Peel-Away Introducer Sheath shall be non-sensitizing.	Passed.
Pyrogenicity (EP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract	18 Fr Peel-Away Introducer Sheath	Passed.

Test	Purpose	Acceptance Criteria	Results
	induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the European Pharmacopoeia.	shall be non-pyrogenic.	
Pyrogenicity (USP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the United States Pharmacopoeia, General chapter <151>.	18 Fr Peel-Away Introducer Sheath shall be non-pyrogenic.	Passed.
Acute systemic toxicity	The purpose of this non-clinical GLP study was to evaluate the acute systemic toxicity of the sodium chloride (SC) test article extract following intravenous (IV) and intraperitoneal (IP) injection in mice. This study was conducted according to ISO 10993-11:2017	There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IV route. There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IP route.	Passed.
18 Gauge Puncture Needle			
Cytotoxicity	The purpose of this GLP study was to	The full strength EMEM10 test article	Passed.

Test	Purpose	Acceptance Criteria	Results
	evaluate the potential cytotoxic effect of a test article extract using an in vitro mammalian cell culture. This study was conducted according to the ISO 10993-5:2009.	extract shall show no cytotoxic potential to L-929 mouse fibroblast cells. 18 Gauge Puncture Needle shall be non-cytotoxic.	
Irritation	The purpose of this non-clinical GLP study was to evaluate the potential of test article extracts to induce local dermal irritation following intracutaneous injection in rabbits. This study was conducted according to the ISO 10993-23:2021.	The difference between each test extract overall mean score and corresponding control blank overall mean score shall be lower than 1.0 (0.0 for the SC and SO test extracts). 18 Gauge Puncture Needle shall be non-irritating.	Passed.
Sensitization	The purpose of this non-clinical GLP study was to evaluate the potential of the test article extracts to cause delayed dermal contact sensitization in the guinea pig. This study was conducted according to the ISO 10993-10:2021.	The topical application of the SC extract shall not induce delayed sensitization in the guinea pig. The topical application of the SO extract shall not induce delayed sensitization in the guinea pig. 18 Gauge Puncture Needle shall be non-sensitizing.	Passed.

Test	Purpose	Acceptance Criteria	Results
Pyrogenicity (EP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the European Pharmacopoeia.	18 Gauge Puncture Needle shall be non-pyrogenic.	Passed.
Pyrogenicity (USP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the United States Pharmacopoeia, General chapter <151>.	18 Gauge Puncture Needle shall be non-pyrogenic.	Passed.
Acute systemic toxicity	The purpose of this non-clinical GLP study was to evaluate the acute systemic toxicity of the sodium chloride (SC) test article extract following intravenous (IV) and intraperitoneal (IP) injection in mice. This study was conducted according to ISO 10993-11:2017	There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IV route. There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IP route.	Passed.

Test	Purpose	Acceptance Criteria	Results
Tunneling Rod			
Cytotoxicity	The purpose of this GLP study was to evaluate the potential cytotoxic effect of a test article extract using an in vitro mammalian cell culture. This study was conducted according to the ISO 10993-5:2009.	The full strength EMEM10 test article extract shall show no cytotoxic potential to L-929 mouse fibroblast cells. Tunneling Rod shall be non-cytotoxic.	Passed.
Irritation	The purpose of this non-clinical GLP study was to evaluate the potential of test article extracts to induce local dermal irritation following intracutaneous injection in rabbits. This study was conducted according to the ISO 10993-23:2021.	The difference between each test extract overall mean score and corresponding control blank overall mean score shall be lower than 1.0 (0.0 for the SC and SO test extracts). Tunneling Rod shall be non-irritating.	Passed.
Sensitization	The purpose of this non-clinical GLP study was to evaluate the potential of the test article extracts to cause delayed dermal contact sensitization in the guinea pig. This study was conducted according to the ISO 10993-10:2021.	The topical application of the SC extract shall not induce delayed sensitization in the guinea pig. The topical application of the SO extract shall not induce delayed sensitization in the guinea pig. Tunneling Rod shall be non-sensitizing.	Passed.
Pyrogenicity (EP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract	Tunneling Rod shall be non-pyrogenic.	Passed.

Test	Purpose	Acceptance Criteria	Results
	induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the European Pharmacopoeia.		
Pyrogenicity (USP)	The purpose of this non-clinical GLP study was to evaluate if a test article extract induced a pyrogenic response following intravenous injection in rabbits. This study was conducted according to the requirements of the United States Pharmacopoeia, General chapter <151>.	Tunneling Rod shall be non-pyrogenic.	Passed.

Test	Purpose	Acceptance Criteria	Results
Acute systemic toxicity	The purpose of this non-clinical GLP study was to evaluate the acute systemic toxicity of the sodium chloride (SC) test article extract following intravenous (IV) and intraperitoneal (IP) injection in mice. This study was conducted according to ISO 10993-11:2017	There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IV route. There shall be no mortality or evidence of systemic toxicity from the SC test article extract injected into mice by the IP route.	Passed.
Smart Charger / Docking Station			
Cytotoxicity	The purpose of this GLP study was to evaluate the potential cytotoxic effect of a test article extract using an in vitro mammalian cell culture. This study was conducted according to the ISO 10993-5:2009.	The full strength EMEM10 test article extract shall show no cytotoxic potential to L-929 mouse fibroblast cells. Smart Charger / Docking Station shall be non-cytotoxic.	Passed.

A.5 Electrical Safety

Table 8 summarizes testing performed to verify that the applicable components of the alfapump® System meet its requirement to comply with the following standards:

Table 8 Electrical Safety testing

Test	Purpose	Acceptance Criteria	Results
Legibility of Marking	To prove that the marking, labels and device labels of the alfapump® System components required by IEC 60601-1:2005/Amd2:2020 are clearly legible.	Testing per IEC 60601-1:2005/Amd2:2020, clause 7.1.2.	Passed.
Durability of marking test	To prove that the marking, labels and device labels of the alfapump® System components required by IEC 60601-1:2005/Amd2:2020 are sufficiently durable to remain clearly legible during the expected service life of the me equipment.	Testing per IEC 60601-1:2005/Amd2:2020, clause 7.1.3.	Passed.
Leakage current	To measure the leakage currents and patient auxiliary currents and to prove that the limits defined by IEC 60601-1:2005/Amd2:2020, clause 8 are not exceed. Measurement of Touch Current (TC), Patient Leakage Current (P), Patient leakage current with mains on the F-type	Testing per IEC 60601-1:2005/Amd2:2020, clause 8.7.	Passed.

Test	Purpose	Acceptance Criteria	Results
	applied parts. Other tests for leakage currents defined by IEC 60601-1:2005/Amd2:2020 are not applicable for the components of the alfapump System.		
Dielectric strength test	To evaluate through a dielectric strength test the capability of solid electrical insulation of the alfapump® System components to withstand the test voltages as specified in Table 6 of IEC 60601-1:2005/Amd2:2020.	Testing per IEC 60601-1:2005/Amd2:2020, clause 8.8.3.	Passed.
Mechanical strength and resistance to heat - Ball pressure test of thermoplastic parts	To evaluate the resistance to heat that shall be retained by all types of insulation during the expected service life of the alfapump® System components.	Testing per IEC 60601-1:2005/Amd2:2020, clause 8.8.4.1.	Passed.
Instability - overbalance in transport position	To prove that the alfapump® System components do not overbalance when placed in any transport position of normal use on a plane inclined at an angle of 10° from the horizontal plane.	Testing per IEC 60601-1:2005/Amd2:2020, clause 9.4.2.1.	Passed.
Instability - overbalance excluding transport position	To prove that the alfapump® System components do not overbalance when placed in any	Testing per IEC 60601-1:2005/Amd2:2020, clause 9.4.2.2.	Passed.

Test	Purpose	Acceptance Criteria	Results
	position of normal use, excluding any transport positions, on a plane inclined at an angle of 5° from the horizontal plane.		
Excessive temperatures	To verify that maximum temperatures do not exceed limits defined by IEC 60601-1:2005/Amd2:2020, clause 11 (Table 22, 23, 24 and RMF for AP).	Testing per IEC 60601-1:2005/Amd2:2020, clause 11.1.1.	Passed.
Spillage, leakage, ingress of water, cleaning, disinfection	To prove that the alfapump® System components ensure a sufficient degree of protection against spillage, leakage, ingress of water or particulate matter, cleaning and disinfection.	Testing per IEC 60601-1:2005/Amd2:2020, clause 11.6.1.	Passed.
Single fault conditions	To prove that the alfapump® System components are designed so that they remain single fault safe.	Testing per IEC 60601-1:2005/Amd2:2020, in accordance with clauses 13.2.2, 13.2.3 and 13.2.12 (other SFCs listed in 13.2 are not applicable).	Passed.
Push Test	To prove that the alfapump® System components are designed to have adequate mechanical strength when subjected to mechanical stress caused by pushing.	Testing per IEC 60601-1:2005/Amd2:2020, clause 15.3.2.	Passed.

Test	Purpose	Acceptance Criteria	Results
Impact Test	To prove that the alfapump® System components are designed to have adequate mechanical strength when subjected to mechanical stress caused by impact.	Testing per IEC 60601-1:2005/Amd2:2020, clause 15.3.3.	Passed.
Drop Test (hand-held and protable)	To prove that the alfapump® System components are designed to have adequate mechanical strength when subjected to mechanical stress caused by dropping.	Testing per IEC 60601-1:2005/Amd2:2020, clauses 15.3.4.1 and 15.3.4.2.	Passed.
Mould Stress Relief	To prove that the alfapump® System components are designed to have adequate mechanical strength when subjected to mechanical stress caused by molding stress relief.	Testing per IEC 60601-1:2005/Amd2:2020, clause 15.3.6.	Passed.
Shock test	To prove that the Smart Charger and Docking Station are designed to have adequate mechanical strength when subjected to mechanical stress and when used in a domestic home environment.	Testing per IEC 60601-1-11:2015/Amd1:2020, clauses 10.1.2.a. and 10.1.3b1.	Passed.
Broad-band random vibration test	To prove that the Smart Charger and Docking Station are designed to have	Testing per IEC 60601-1-11:2015/Amd1:2020,	Passed.

Test	Purpose	Acceptance Criteria	Results
	adequate mechanical strength when subjected to mechanical vibration and when used in a domestic home environment.	clause. 10.1.2.b and 10.1.3c.	

A.6 Electromagnetic Compatibility (EMC)

Error! Reference source not found. summarizes testing performed to verify that the applicable components of the alfapump® System meet its requirement to comply with the following standards:

Table 9 Electromagnetic Compatibility (EMC) testing

Test	Purpose	Acceptance Criteria	Results
Active non-implantable alfapump® System components			
Radiated RF emissions	To verify that conducted Radiated RF emissions produced by external electrical components of the alfapump® System meet the acceptability criteria defined by CISPR 11 (2003).	Testing per CISPR 11 (2003) Industrial, Scientific, and Medical Equipment – Radio Frequency Disturbance Characteristics – Limits and Methods of Measurements. Group 1, Class B Limit Radiated Emissions; 30 MHz to 1 GHz.	Passed.
Conducted Emissions	To verify that conducted emission produced by external electrical components of the alfapump® System meet the acceptability criteria defined by CISPR 11 (2003).	Testing per CISPR 11 (2003) Industrial, Scientific, and Medical Equipment – Radio Frequency Disturbance Characteristics – Limits and Methods of Measurements. Group 1 and Group 2, Class B limits; 150 kHz to 30 MHz.	Passed.
Electrostatic Discharge	To verify that external electrical components of the alfapump® System are able to withstand electrostatic discharge.	Testing per IEC 61000-4-2:2008. No degradation shall be observed as result of the test at: • ± 8 kV contact ± 2 kV, ± 4 kV, ±8 kV, ± 15 kV air	Passed.
Electrical Fast Transient	To verify that external electrical components of the alfapump® System are able to withstand disturbance generated by electrical fast transient phenomena and bursts.	Testing per IEC 61000-4-4:2012. No degradation shall be observed as result of the test at: • ± 2 kV for power supply lines ± 1 kV for USB lines	Passed.
Surge	To verify that external electrical components of the alfapump® System are able to withstand surge disturbance.	Testing per IEC 61000-4-5:2005. No degradation shall be observed as result of the test at: L-N:± 1 kV	Passed.
Power Frequency Magnetic Field	To verify that external electrical components of the alfapump® System are able to withstand disturbance generated by power frequency magnetic field.	Testing per IEC 61000-4-8:2009. No degradation shall be observed as result of the test at: 30 A/m	Passed.

Table 10 Electromagnetic Compatibility (EMC) testing (continued)

Test	Purpose	Acceptance Criteria	Results
Voltage dips,short interruptions on power supply input lines	To verify that external electrical components of the alfapump® System are able to withstand voltage dips, short interruptions on power supply input lines.	Testing per IEC 61000-4-11:2004. No degradation shall be observed as result of the test at: • Voltage dips: o 0% UT (0.5 cycle) at 0°, 45°, 90°, 135°, 180°, 225°, 270°, 315° o 0% UT (1 cycle) and 70% UT (25/30 cycles) at 0° • Voltage interruptions: 0% UT (250/300 cycles)	Passed.
Radiated Fields in Close Proximity	To verify that external electrical components of the alfapump® System are able to withstand disturbance generated by radiated fields.	Testing per IEC 61000-4-39:2017. No degradation shall be observed as result of the test at: • 8 A/m at 30 kHz • 65 A/m at 134.2 kHz 7.5 A/m at 13.56 mHz	Passed.
Proximity fields from RF wireless communication equipment	To verify that external electrical components of the alfapump® System are able to withstand disturbance from proximity fields generated by RF wireless communication equipment.	Testing per IEC 61000-4-3:2006 / Amd1:2007 / Amd2:2010). No degradation shall be observed as result of the test at: 30V/m (Test frequencies and levels (9 to 28 V/m) as specified in Table 9 of IEC 60601-1-2)	Passed.

Table 11 Electromagnetic Compatibility (EMC) testing cont.

Test	Purpose	Acceptance Criteria	Results
Proximity magnetic field	To verify that external electrical components of the alfapump® System are able to withstand magnetic field influences.	Testing per IEC 60601-1-2:2014 (as specified in Table 11 using the test methods specified in IEC 61000-4-39). No degradation shall be observed as result of the test at: 9 kHz to 13.56 MHz	Passed.
Radiated Immunity	To verify that external electrical components of the alfapump® System are able to withstand disturbance related to radiated immunity.	Testing per IEC 61000-4-3:2006 / Amd1:2007 / Amd2:2010). No degradation shall be observed as result of the test at: 10 V/m at 80 MHz to 2,7 GHz	Passed.
Conducted Immunity	To verify that external electrical components of the alfapump® System are able to withstand disturbance related to conducted immunity.	Testing per IEC 61000-4-6:2013. No degradation shall be observed as result of the test at: • 150 kHz to 80 MHz, 3Vrms (outside ISM) 6Vrms (ISM and amateur radio bands)	Passed.

Table 12 Electromagnetic Compatibility (EMC) testing cont.

Test	Purpose	Acceptance Criteria	Results
Active implantable alfapump			
Protection from static magnetic fields	To verify that alfapump® is able to withstand disturbance from static magnetic fields.	No degradation shall be observed as result of the test performed according to ISO 14708-7:2019, Clause 27.1.	Passed.
Radiated magnetic field test for frequencies 16,6 Hz to 27 MHz	To verify that alfapump® is able to withstand disturbance from radiated magnetic fields.	No degradation shall be observed as result of the test performed according to ISO 14708-7:2019, Clause 27.2.	Passed.
Radiated electric field test for frequencies 10 MHz to 2,7 GHz	To verify that alfapump® is able to withstand disturbance from radiated electric fields.	No degradation shall be observed as result of the test performed according to ISO 14708-7:2019, Clause 27.3.	Passed.

A.7 Federal Communications Commission (FCC)

Table 13 summarizes testing performed to verify that the applicable components of the alfapump® System meet its requirement to comply with the following FCC Regulation:

- Radio frequency testing according to FCC Part 15, Part 22 and 24
- Emission test according to FCC Part 18
- Specific Absorption Rate (SAR)

Table 13 FCC testing

Test	Purpose	Acceptance Criteria	Results
alfapump® System FCC testing	To evaluate the RF output radiated power and the transmitter radiated unwanted emissions of the alfapump System	Testing per applicable requirements of FCC Part 15.249 and FCC Part 22 and 24, FCC Part 18.	Passed.

A.8 Wireless Coexistence Testing

Table 14 summarizes testing performed to verify wireless functional performance with key performance indicators of the QoS to demonstrate that the alfapump® System was not detrimentally affected by simulated radiofrequency radiation representative of RFID readers.

Furthermore, the EMC testing for alfapump® System evaluating interference from RF wireless communication in close proximity to alfapump® System at spot frequencies from Table 9 of IEC 60601-1-2:2014/Amd1:2020 did not lead to any communication issues or unacceptable risks. The EMC of the wireless signals was tested accordance with FCC Part 15 and FCC Part 18 with acceptable results.

Table 14 Wireless Coexistence testing

Test	Purpose	Acceptance Criteria	Results
Wireless Coexistence Testing	To assess the ability of the Smart Charger P5 and alfapump to successfully maintain their functional wireless performance (FWP) while reaching acceptable values of selected Key Performance Indicators (KPIs): Received Signal Strength Indicator ((RSSI) level, Packet Error rate, and Time to complete request) in the presence of unintended signals that are likely to be found in the same operating environment.	Testing per applicable requirements of IEEE ANSI C63.27:2021.	Passed.

A.9 Packaging and Shelf-life Testing

Table 15 summarizes testing performed to verify the packaging as well as functional testing over the shelf life of alfapump® System to comply with the ISO 11607-1:2019: "Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems"; ISO 11607-2:2019: "Packaging for terminally sterilized medical devices -- Part 2: Validation requirements for forming, sealing and assembly processes."

An 18-month (1.5 years) shelf-life has been substantiated for alfapump® System's sterile barrier systems based on accelerated aging tests. Product specifications, quality, functionality, and safety requirements were demonstrated after sterilization and accelerated aging. The real time aging packaging studies are still ongoing.

Table 15 Packaging and Shelf-life testing

Test	Purpose	Acceptance Criteria	Results
Packaging Validation Test	To demonstrate that the two carton boxes give protection to the products during transportation of the alfapump® System.	Visual Inspection Testing per ASTM F1886/F1886M-16. Seal Strength Testing per ASTM F88/F88M-23. Bubble Leak Testing per ASTM F2096-11(2019).	Passed.

A.10 Life-time Testing

Table 16 summarizes Life-time testing performed to demonstrate through an accelerated aging model that the alfapump® has a lifetime of up to two years. This Accelerated Aging Life Test is intended to be a failure terminated test, where the systems are tested until

failure or until the foreseen Accelerated Aging Time of 52.40 days = 1.75 months equivalent to two years of real time is reached. In this submission, both accelerated aging and real-time aging data is submitted to support the life-time of up to two years.

Table 16 Life-time testing

Test	Purpose	Acceptance Criteria	Results
alfapump® System Lifetime Testing	To demonstrate through an accelerated aging model that the alfapump and implant accessories have a lifetime equivalent of up to two (2) years.	alfapump® System must be fully functional for up to 2 years. Full functionality is defined based on the ability of the alfapump® System to perform its intended use.	Passed.

A.11 Software Verification

Table 17 summarizes Software verification and validation testing for alfapump® System performed in accordance with IEC 62304:2006/Amd1:2015 and documentation is provided for Enhanced Level as recommended in FDA's guidance for Industry and FDA Staff, "Content of Premarket Submissions for Device Software Functions" (June 14, 2023).

Table 17 Software verification

Test	Purpose	Acceptance Criteria	Results
Software verification and validation testing	To demonstrate that the software specifications implemented for each software component conform to user needs and intended use and that the particular software requirements have been implemented and are traceable to system requirements.	Testing per applicable requirements of IEC 62304:2006/Amd1:2015.	Passed.

A.12 Cybersecurity

A cybersecurity analysis was performed for the alfapump® System per the recommendations in the FDA guidance for Industry and FDA Staff, "Content of Premarket Submissions for Management of Cybersecurity in Medical devices" (September 27, 2023), and the principles outlined in the FDA guidance for Industry and FDA Staff, "Postmarket Management of Cybersecurity in Medical Devices" (December 28, 2016).

Cybersecurity threat modeling, risk assessment, and controls and security testing (including penetration testing) were performed to comply with requirements specified in Section 524B(b)(2) of the Federal Food, Drug, and Cosmetics Act to provide a reasonable assurance that the alfapump® System with its wireless capabilities is cybersecure.

B. Animal Studies

Not applicable – no animal studies have been performed.

C. Additional Studies

Not applicable – no additional studies have been performed.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed a clinical study to establish the reasonable assurance of safety and effectiveness of the alfapump® System intended for single patient use only in adult patients with refractory or recurrent ascites due to liver cirrhosis. It is indicated for the removal of excess peritoneal fluid from the peritoneal cavity into the bladder, where it can be eliminated through normal urination. In the US, the device was evaluated under IDE # G140126. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The POSEIDON Trial was the pivotal clinical trial for this PMA. POSEIDON wasa multicenter, single arm within subject crossover design pivotal trial conducted in patients diagnosed with refractory or recurrent ascites due to liver cirrhosis who met inclusion/exclusion criteria. The study aimed to enroll up to 70 pivotal cohort patients and implant a maximum of 50 pivotal cohort subjects with refractory or recurrent ascites at up to 20 sites. In addition, up to 45 additional enrolled roll-in patients and a maximum of 40 implanted roll-in patients were allowed.

The study report provides the results of the pre-specified analysis of a minimum of 40 treated pivotal cohort patients through 6 months. A total of 71 subjects were enrolled in the pivotal cohort, with 40 subjects receiving the alfapump®. In the roll-in cohort, 40 subjects were enrolled, with 29 subjects receiving the implant.

Patients were treated (implanted) between 11 October 2019 and 31 March 2022, inclusive of both pivotal and roll-in cohorts. The database for this PMA reflected data collected through 01 November 2023 and included 40 implanted pivotal cohort patients and 29 implanted roll-in patients. There were a total of 15 implanting investigational sites.

Patients are being followed for longer-term safety and effectiveness for a total of 24 months post-implant **Figure 2.** Patients with a functioning pump at 24 months can consent to continued participation in a long-term follow-up evaluation with assessments every 6 months, from 24 months post-implant through the time the pump ceases to function, pump explant or patient death. This long-term follow-up period will continue until the product is approved or the sponsor determines they will no longer pursue product approval.

The study included two cohorts:

- **Roll-in Cohort Patients:** In the study centers without previous experience in alfapump® placement, training in the alfapump® implant procedure was conducted first. Roll-in patients were enrolled at the site until sufficient experience was obtained and the site was approved by the sponsor to treat patients in the pivotal phase. The goal was to compile a pivotal study patient population in which the results were independent of any learning curve. Up to 3 roll-in patients per site were planned. Additional roll-in patients were allowed if there was a change in principal investigator (PI) or radiologist. Roll-in patients did not undergo the 3-month pre-implant observation period and are not included in the Primary Analysis set but are summarized separately for purposes of a comprehensive safety evaluation, with effectiveness data provided as supplemental information.

- **Pivotal Cohort Patients**: Pivotal cohort patients were evaluated in a 3-month pre-implant observation period during which they received standard of care therapy consisting of paracentesis as required for removal of ascitic fluid. Following the initial 3-month observation period during which the number and volume of paracentesis and quality of life (assessed by general quality of life scores such as SF-36), as well as disease-specific validated questionnaires (Ascites-Q), were documented, patients were re-evaluated for eligibility for pump implant.

All patients (pivotal and roll-in) underwent a final eligibility assessment prior to pump implant. If deemed eligible, patients were implanted with the alfapump®. In the 3 months post-implant (Day 0 to Day 90), patients were monitored with pump adjustments as needed to increase or decrease volume of fluid to be removed each day (referred to as *stabilization period*). Pump adjustments could only be made in-person in the clinic. The PI or sub-investigator were responsible for determination of pump-setting adjustments.

After this period of stabilization, a 3-month observation period (Day 91 to Day 180) began (referred to as post-implant *observation period*). In each period, the protocol specifies when symptom-driven (therapeutic) paracentesis could be performed per protocol, as well

as conditions under which the use of diuretics could be considered (all patients were required to discontinue diuretics following alfapump® implantation).

The study was designed to demonstrate in pivotal cohort patients:

1) a 50% reduction in the per-patient ratio of post-implant 3-month observation period (month 4 to month 6 post-implantation) to pre-implant 3-month observation period with respect to average monthly requirement for therapeutic paracentesis, and

2) at least 50% of patients achieved a 50% reduction in the frequency for therapeutic paracentesis in the same period.

As described in the study protocol, the pre-implant observation period reflected Day -90 to Day -1 (days prior to implant, referred to as *pre-implant period*) and the post-implant observation period reflected Day 91 to Day 180 post-implant (post-implant observation period; Day 0 to Day 90 represented a period of pump adjustment and stabilization post-implant).

Statistical Methods

Sample size calculation and Hypothesis for the Co-Primary Effectiveness Endpoint

The null and alternative hypothesis for the per-patient ratio endpoint are:

H_0: $\mu \geq 0.50$

H_a: $\mu < 0.50$

Based on data from a previous feasibility study with the alfapump® System assuming $\mu = 0.2$, $\sigma = 0.192$, one-sided $\alpha=0.025$, and 80% power a total of 6 evaluable patients is required.

The null and alternative hypothesis for the percent of patient with a 50% reduction is:

H_0: $p_T \leq 0.50$

H_a: $p_T > 0.50$

Based on data from a previous feasibility study with the alfapump® System assuming $p_T = 0.75$, one-sided $\alpha=0.025$, and 80% power a total of 29 evaluable patients is required.

Taking both primary endpoints into account and assuming 20% lost to follow-up rate. A minimum of 37 enrolled patients was required to demonstrate statistical success (i.e. 50% reduction of number of therapeutic paracentesis post implant).

Statistical Methods and Analyses

Statistical Analyses for this study are based on the Frequentist Approach. Formal statistical testing was carried out for the co-primary effectiveness endpoints and prespecified secondary endpoints, at a one-sided 0.025 level of significance. Testing followed a hierarchical gatekeeping approach. If both primary co-primary endpoints were met, the prespecified secondary endpoints were tested in a serial order to control for a type I error rate at 0.5. Both primary effectiveness endpoints needed to be met at the 0.025 level for study success to be achieved.

All other variables are summarized with the descriptive statistics. Categorical data are presented using frequencies and percent of patients in each category. Continuous data are presented using mean, standard deviation, median, minimum, maximum, and sample size. roll-in patients are presented separately from pivotal cohort patients.

The primary analysis was conducted in the modified intent-to-treat population (mITT) which included patients who signed the informed consent form and in whom an attempt to implant the alfapump® System occurred.

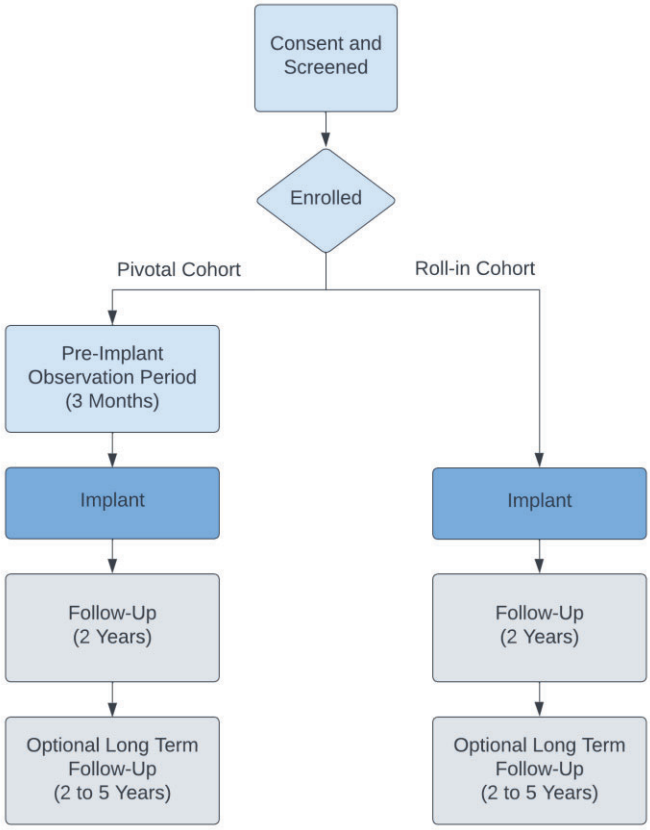
Analysis of the co-primary endpoints used imputation to account for missing data for all patients who did not complete the post implant observation period (i.e. did not reach day 180 without death, explant or exit for other reason) in accordance with the agreed upon imputation plan described in the clinical protocol. Specifically, a combination of worst-case scenario imputation, best-case scenario imputation and multiple imputation was utilized depending on the reason for missingness. Multiple imputation was completed with a monotone linear regression to impute the number of post-implant therapeutic paracenteses. Available data was used for all other analyses.

Data for the per-patient ratio were non-normally distributed, so the endpoint was tested using a Wilcoxon signed-rank test. The proportion of subjects with >50% reduction in therapeutic paracentesis endpoint was tested using the one sample exact binomial test of proportions. Data for the prespecified secondary endpoints were normally distributed and tested using a paired t-test. All endpoints were calculated at a one-sided $\alpha = 0.025$.

The combined safety event rates for the safety end point were calculated along with a two-sided exact 95% confidence interval.

Error! Reference source not found. provides a summary of the study design for the POSEIDON trial and Error! Reference source not found. provides the full Schedule of Assessments (SOA). A detailed summary of study and results is included in the sections below.

Figure 2: POSEIDON Trial Study Design



Error! Reference source not found.**4** provides a summary of the study design for the POSEIDON trial. A detailed summary of study and results is included in the sections below:

Table 14. Summary of the study design for the POSEIDON trial

Study Design	alfapump® System in the treatment of refractory or recurrent ascites: a multicenter single arm within subject crossover design pivotal study
Number of Sites	Up to 20 across North America (USA and Canada)
Number of Patients	Up to 70 enrolled patients with a maximum of 50 pivotal cohort implants and a minimum of 40 patients through 6 months were planned to be included in the pivotal trial. Up to an additional 45 enrolled roll-in patients and a maximum of 40 implanted roll-in patients were planned.
Study Objective	The study was designed to collect and analyze data to assess: ▪ Effectiveness of the alfapump® to control ascites as determined by the reduction in the need for repeated paracentesis compared to baseline ▪ Safety of the alfapump® implant procedure and alfapump® therapy as determined by rates of explant, reinterventions, and other serious device or procedure related adverse events ▪ Patient Reported Outcomes (assessed by SF-36 PCS) as well as a disease-specific validated questionnaire (Ascites- Q) ▪ Health Resource Utilization as determined by economic analysis

Table 15: Schedule of Activities

	Pivotal only																			
	Pre-Implant						Post-Implant													
	Screening / Consent	Baseline assessment	Pre-Implant Observation	Pre-Implant Observation Period End	Day -1 Pre-Implant	Pump Implantation	Pre-Discharge (7 days)	Day 14	Day 30 - 1 month	2 month follow-up	3 month follow-up	6 month follow-up	9 month follow-up	12 month follow-up	15 month follow-up	18 month follow-up	21 month follow-up	24 month follow-up	Long Term follow-up Every 3 Months (Optional) [2]	Unscheduled Visit
		[12]	Observation every 2 weeks for 90 days	-30 Days to Day 0	-2Days to -a Days	Day 0	Discharge / D7 [3]	Day 14 +/- 5D	1 Month +/- 10D	2 Months +/- 14D	3 Months +/- 14D	6 Months +/- 30D	9 Months +/- 45D	12 Months +/- 45D	15 Months +/- 45D	18 Months +/- 60D	21 Months +/- 45D	24 Months +/- 45D	X	X
Consent	X																			
Medical / Social Assessment		X																		
Concomitant medications		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy test (women)	X				X															
Frailty assessment		X			X [10]						X	X		X				X		
Abdominal and renal-bladder ultrasound and if required, urodynamic assessment	X	X			X [4]															
Abdominal/pelvic CT scan		X												X				X		
Paracentesis		X	X (PRN)	X (PRN)	X															
Diagnostic paracentesis[5]					X															
Urine culture [8]					X		X	X	X	X	X	X						X		
Urinalysis [9]					X		X	X	X	X	X	X						X		
Body weight (kg) [11]		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine Labs [6]	X	X (optional)	X (monthly)	X	X [1]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Albumin Infusions					X	X		X	X											
Vital Signs monitoring / physical assessment		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Scales		X		X	X [10]				X		X	X		X		X		X		
Diary [7]			X								X									
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prophylactic antibiotics						X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Implantation						X														
Resource Utilization		X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X

[1] PTT required on Day-1 Pre-implant assessment.
[2] Optional Long Term Follow-up Evaluation through the time the pump ceases to function, pump explant, patient, patient death or product approval or decision by the sponsor to no longer pursue approval.
[3] Discharge/D7: Whichever comes first.
[4] May be conducted up to 2 months prior to implant.
[5] Ascites fluid cell count to be done pre-implant to exclude SBP.
[6] Routine Labs: Bilirubin, Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Total Protein, Albumin, Glucose, C-reactive protein, Globulin, Sodium, Potassium, Urea/BUN, Creatinine, Calcium, eGFR, Full Blood Count (FBC), Prothrombin time (secs or %) and INR. Prealbumin required at Screening, Preimplant (Day-1) and 1,2,3,6,12, and 24 months.
[7] Diary assessment completed during the 1st Month of observation period and one month at 3-4 months.
[8] Urinalysis completed Day 2 and Day 7 if applicable to exclude infections.
[9] Urine Culture completed Day 2 and Day 7 if applicable to exclude infections.
[10] Repeat prior to implant (up to 30 months prior to implant is acceptable) for pivotal cohort patients if implant is > 120 days since baseline assessment.
[11] Patient is to self monitor body weight at a minimum weekly and report fluctuations exceeding 5lbs in a week or 2-3lbs in a day.
[12] - 120 to -90 Days (Pivotal) prior to Implant Date, or no more than -60 Days (Roll In) prior to Implant.

Note: Recommendation for weekly phone check ins post pump implantation.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the POSEIDON study was limited to patients who met the following inclusion criteria:

1. Patients > 18 years of age.
2. Cirrhosis of the liver defined by histological and/or clinical, endoscopic, laboratory, and radiological criteria.
3. Refractory or recurrent ascites primarily managed with periodic therapeutic paracentesis[1]. Patients must have a minimum of 2 therapeutic paracenteses in the 30 days prior to enrollment.
4. Not a candidate for (*e.g.* refused, contraindicated) transjugular intrahepatic portosystemic shunt (TIPS) or previously implanted TIPS is permanently obstructed or non-functioning.
5. Screened for esophageal varices and on optimal management.
6. Absence of contraindications to prophylactic antibiotic use from time of pump implant.
7. Life expectancy of at least 6 months following pump implant (approximately 10 months from enrollment).
8. Capable of giving written informed consent, willing to comply with study procedures including the 3-month pre-implant observation period and ability to operate and charge the device.
9. Women of childbearing age should use adequate contraceptives.

Reassessed at time of implant procedure (pivotal cohort only):

10. Has required a minimum of 5 therapeutic paracenteses in the 3-month observation period prior to pump implant.

Patients were not permitted to enroll in the POSEIDON study if they met any of the following exclusion criteria:

At the time of initial screening:

1. Renal failure defined as serum creatinine higher than 1.5 mg/dL.
2. More than one episode of spontaneous bacterial peritonitis over the previous 6 months.
3. More than one episode of bacterascites over the previous 6 months.
4. Recurrent urinary infections as per standard criteria, defined as 2 or more episodes over the last 6 months.
5. Evidence of loculated ascites, as per imaging.
6. Hepatocellular carcinoma, exceeding Milan criteria or for which RF ablation is anticipated.
7. Pregnant females or females anticipating pregnancy during study period.
8. Patients currently enrolled in another interventional clinical study that has not reached the primary endpoint assessment point, or (for pivotal cohort) patients who have previously had an alfapump implanted.

[1] Therapeutic paracentesis is defined as removal of at least 1.5L of ascitic fluid by means of percutaneous drainage with therapeutic intent in patients with symptoms related to fluid accumulation or clear evidence of ascites accumulation (weight gain, abdominal circumference), excluding patients receiving a puncture for diagnostic purpose only.

9. Immuno-modulatory treatment (including azathioprine, methotrexate, anti-TNF therapies) used within last 4 months (corticosteroids at stable dose over the last 4 months but < 15 mg/day, or in tapering doses were allowed).
10. Known or suspected hepatic or extra hepatic malignancy (other than skin cancer and in-situ cancers), unless adequately treated or in complete remission for ≥ 3 years.
11. History of bladder cancer.
12. BMI > 40 presenting a risk for technical difficulties for surgery or catheter implantation.
13. Contraindications to general anesthesia.
14. Comorbid condition or other reason (example hypertension) that may preclude stopping diuretics after enrollment.
15. MELD-Na (Model of End-Stage Liver Disease Sodium) Score > 20.
16. Budd Chiari syndrome (pivotal cohort only).
17. Clostridium difficile infection within the past year.

Assessed or re-assessed at time of pump implant:

18. Acute gastrointestinal hemorrhage requiring transfusions over the previous 42 days.
19. Condition that prevents continued cessation of diuretic use.
20. Patient condition did not allow the implant procedure to be performed within the limits of acceptable risk (*e.g.* cardiovascular comorbidities, variceal bleeding within the previous 6 weeks, skin infections or skin ulcers of the anterior abdominal wall within 2 weeks of device placement).
21. Hepatocellular carcinoma exceeding Milan criteria or for which RF ablation is anticipated.
22. Intensive Care Unit (ICU) admission in the 30 days preceding pump implant procedure.
23. INR ≥ 2.0.
24. Platelet count of < 50,000 / μL at the time of implantation, unless the platelet count was ≥30,000 / μL and bleeding risk could be satisfactorily addressed with means such as platelet infusion during the procedure and/or thrombopoietin agonists.
25. Bacterial peritonitis within 4 weeks of implant procedure (this includes peritonitis diagnosed at the time of intervention). Note: at the time of final eligibility (just prior to implantation) the subject was not allowed to move forward with the procedure if he/she had experienced an episode of SBP within four weeks of the implant procedure date.
26. Bacterascites within 4 weeks of implant procedure (this includes bacterascites diagnosed at the time of intervention). Note: at the time of final eligibility (just prior to implantation) the subject was not allowed to move forward with the

procedure if he/she had experienced an episode of bacterascites within four weeks of the implant procedure date.

27. Serum sodium < 125 mmol/L.
28. Urinary infection within the last 2 weeks.
29. Obstructive uropathy, residual urinary volume exceeding 100 ml, or any bladder anomaly which might contraindicate implantation of the device.*)*
30. Evidence of renal failure, defined as serum creatinine higher than 1.5 mg/dL.
31. Evidence of loculated ascites, as per imaging.
32. Pregnant females or females anticipating pregnancy during study period

2. Follow-up Schedule

All patients were scheduled to undergo follow-up examination daily through discharge, and then at 14 ± 5 days, 1 month ± 10 days, 2 months ± 14 days, 3 months ± 14 days, 6 months ± 30 days, 9 months ± 30 days, 12 months ± 45 days, 15 months ± 45 days, 18 months ± 45 days, 21 months ± 45 days, and 24 months ± 45 days postoperatively. Patients who elected to participate in the optional long term follow up return for follow-up examination every 3 months (+/- 45 days) between month 24 and the time when end of study is declared.
Preoperatively, patients underwent a screening assessment, including medical history and physical assessment, routine labs, and evaluation of paracentesis history. Patients eligible for enrollment underwent further baseline assessments, including Frailty, Abdominal/Pelvic CT, abdominal and renal bladder ultrasound, Quality of Life (SF-36, Ascites-Q), Routine Labs, Health resource Utilization and Medication review. Pivotal cohort patients underwent a 90-day pre-implant observation period including monthly labs, assessment of paracentesis requirement and adverse events, pre- and post-observation period SF-36 and Ascites-Q, and a 30-day Daily Diary Assessment of symptoms. Postoperatively, the objective parameters measured during the study included Physical Assessment, Routine Labs, Paracentesis requirement, health resource utilization, Medication review, Urinalysis and Urine culture (Day 14 then 1, 2, 3, 6 and 24 months), Abdominal/Pelvic Computer Tomography (CT) (12 and 24 months), Frailty Assessment (3, 6, 12 and 24 months), SF-36 and Ascites-Q Questionnaires (1, 3, 6, 12, 18 and 24 months), and daily diary assessment of ascites symptoms for 30 days between month 3 and 4 post-implant. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints
With regards to safety, the primary safety endpoints are as follows:

Primary Safety Endpoint:
Combined rate of open surgical reintervention (requiring general anesthesia or laparotomy) due to pump system-related adverse event (AE) or to restore pump functionality, pump explant (without replacement) due to pump system-related

adverse event, or pump system-related death from time of pump implant through 6 months post-implant (as adjudicated by the Clinical Events Committee (CEC)).

With regards to effectiveness, the primary safety endpoints are as follows:

Primary Effectiveness Endpoints
Comparing data from the post-implant 3-month observation period to data from the pre-implant 3- month observation period):

- Per-patient ratio of post-implant to pre-implant with respect to average monthly number of therapeutic paracentesis (defined as removal of ascites ≥1.5L through needle puncture of abdominal wall).
- Proportion of patients with at least 50% reduction in number of therapeutic paracenteses from the pre-observation period to post-observation period.

Secondary *Effectiveness E*ndpoints
Intended for label claim and tested using an approach which controls type I error across the tested endpoints:

- Requirement for large volume paracentesis (LVP): reduction in the average number of LVP events per month (that consist of removing ≥ 5L of ascitic fluid) in the post-implant 3-month primary endpoint observation period compared to the pre-implant observation period.
- Reduction of cumulative volume of ascitic fluid removed by means of therapeutic paracentesis in the post-implant 3-month primary endpoint observation period as compared to the pre-implant 3-month observation period.
- Improvement in SF-36 Physical Component Score in the post-implant 3-month primary endpoint observation period as compared to the pre-implant 3-month observation period.
- Improvement in Ascites-Q Score in the post-implant 3-month primary endpoint observation period as compared to the pre-implant 3-month observation period.

With regard to success/failure criteria, individual patient success is defined as a 50% reduction in the average monthly requirement for therapeutic paracentesis in the post-implant 3-month observation period (month 4 to month 6 post-implantation) compared to the pre-implant 3-month observation period with respect to average monthly requirement for therapeutic paracentesis. For study success, both primary effectiveness endpoints must be met with a significance level of 0.025.

B. Accountability of PMA Cohort

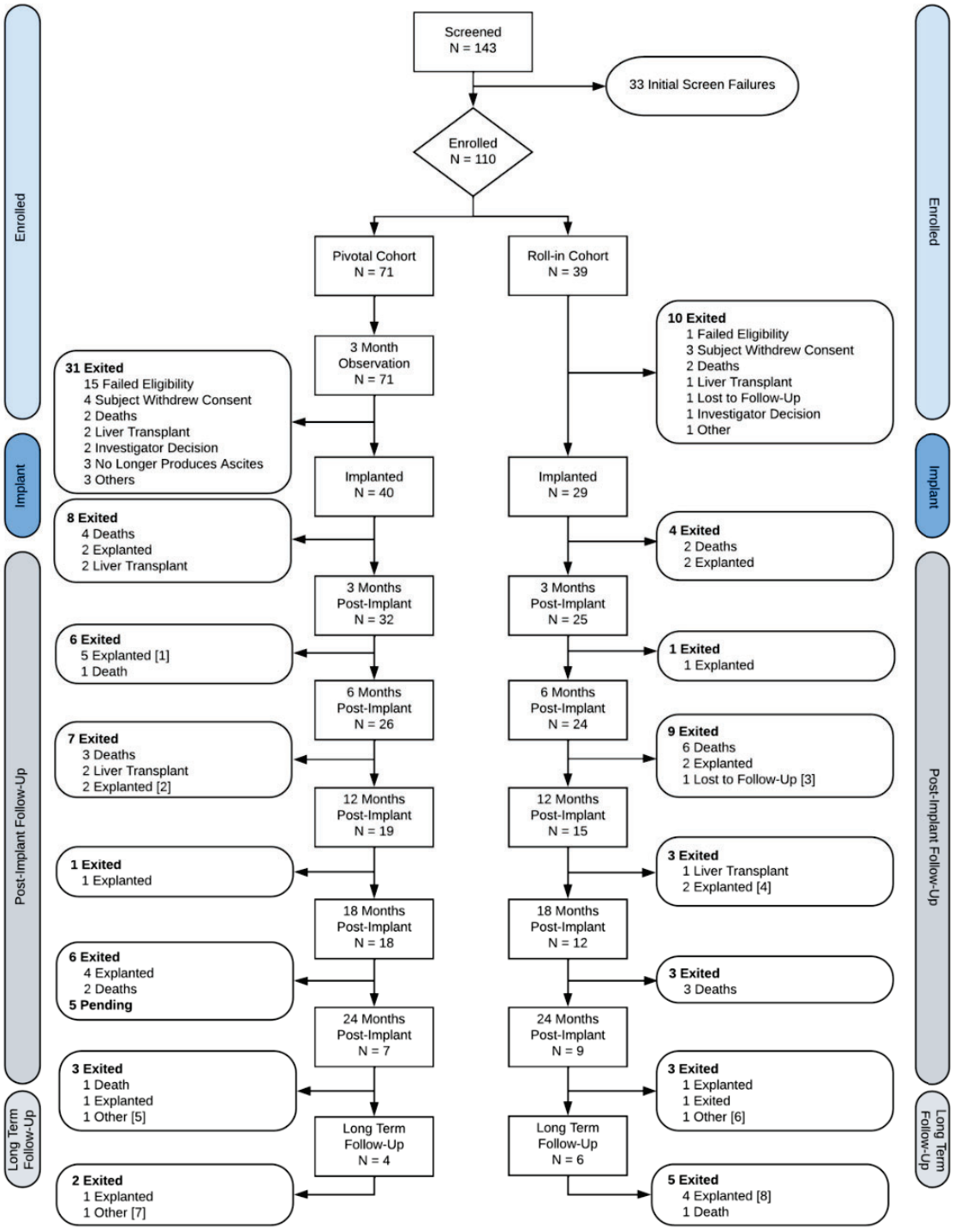
A CONSORT diagram summarizing patient status in the POSEIDON trial is presented in

Figure . A total of 143 patients were screened, of which 110 patients were enrolled, 71 patients in the pivotal cohort and 39 patients in the roll-in cohort.

Pivotal cohort: Of the 71 patients that were enrolled in the pivotal cohort, 40 patients were implanted with the alfapump®. Thirty-one (31) patients exited the study before implant, the most common reason being failing eligibility criteria (15 patients). Thirty-two (32) of the 40 implanted patients (80%) completed the 3-month follow-up visit, 26 patients (65%) completed the 6-month follow-up visit, and 19 patients (47.5%) completed the 12-month follow-up visit. While follow-up is ongoing, 7 patients (17.5%) completed the 24-month follow-up visit and 4 patients (10%) completed a visit in the long-term follow-up.

Roll-in cohort: Of the 39 patients enrolled in the roll-in cohort, 29 patients were implanted with the alfapump®. Ten (10) patients exited the study before implant. Twenty-five (25) of the 29 implanted patients (86.3%) completed the 3-month follow-up visit, 24 patients (82.8%) completed the 6-month follow-up visit, and 15 patients (51.7%) completed the 12-month follow-up visit. While follow-up is ongoing, 9 patients (31.0%) completed the 24-month follow-up visit and 6 patients (20.7%) continued in the optional long-term follow-up.

Figure 4 POSEIDON Subject Disposition – Pivotal and Roll-in Cohorts



Note: "Pending" indicates patient is still actively enrolled and awaiting next visit (implant or follow-up). Explanted patients can be re-implanted if eligible.
[1] Patient 02-002 never had a 6-month visit, was explanted 111 days post-implant, then subsequently died 183 days post-implant.

[2] Patient 02-011 was explanted 317 days post-implant, then subsequently died 320 days post-implant.
[3] Patient 05-001 was lost to follow-up and did not consent to the long-term follow-up so was considered exited however the site relayed that the patient resurfaced and was explanted after 2 years with the device in place.
[4] Patient 10-001 was explanted 458 days post-implant, then subsequently died 485 days post-implant.
[5] Patient 01-019 exited the study and was never explanted.
[6] Patient 01-001 was explanted 280 days post-implant but was followed through 24 months.
[7] alfapump for patient 01-013 ceased to function. Patient was exited to be entered into special access program for pump exchange.
[8] Patients 01-007 and 05-003 had re-implants. Patient 01-007 was first explanted on day 10, re-implanted on day 280, then explanted again and exited on day 987 post-implant. Patient 05-003 was first explanted on day 254, re-implanted on day 433, then explanted again and exited on day 821 post-implant.

C. Study Population Demographics and Baseline Parameters

Patient demographics are shown in **Table** . Age and gender distribution of the included patients are similar to the patient population with liver cirrhosis [17].

Table 16 Demographics and Baseline Characteristics - Pivotal

	Pivotal mITT Population N = 40
Age (years)	
Mean ± *SD (N)	63.6 ± 9.49 (40)
Median (Min, Max)	64.0 (42.0, 83.0)
Sex	
Male	65.0% (26/40)
Female	35.0% (14/40)
Ethnicity	
Hispanic or Latino	10.0% (4/40)
Not Hispanic or Latino	87.5% (35/40)
Not Reported	0.0% (0/40)
Unknown	2.5% (1/40)
Race	
American Indian or Alaska Native	0.0% (0/40)
Asian	2.5% (1/40)
Black or African American	2.5% (1/40)
Native Hawaiian or Other Pacific Islander	0.0% (0/40)

	Pivotal mITT Population N = 40
White	95.0% (38/40)
Other	0.0% (0/40)
Multiple	0.0% (0/40)

Source Table 2.1; * Standard Deviation

Relevant medical history is shown in **Table 1**. Alcohol substance abuse was reported in 52.5% (21/40) of patients of which 42.5% (17/40) were in the past and had resolved. Current chronic kidney disease was reported in 10% (4/40) of the patients. Twenty-one (21) patients, more than half of the pivotal study cohort, had current diabetes, of which 9 required insulin (22.5%, 9/40). Comorbidities such as diabetes may increase the risk of complications in patients with liver cirrhosis [18, 19]. Other relevant medical history was reported in 57.5% (23/40) of the patients, including abdominal and umbilical hernias, hypotension, hypertension, hyperlipidemia, gastro-esophageal reflux disease (GERD), sleep apnea, obesity, anemia, electrolyte abnormalities and prior surgical procedures.

In the 3 months prior to enrollment, 25% of patients had required hospitalization, with a mean number of hospitalizations in the 3 months prior to enrollment in these patients of 1.1 ± 0.32.

Table 17 Medical History – Pivotal mITT

	Pivotal mITT Population N = 40
Alcohol/Substance Abuse	52.5% (21/40)
Current	10.0% (4/40)
Past, Resolved	42.5% (17/40)
Congestive Heart Failure	7.5% (3/40)
Current	7.5% (3/40)
Past, Resolved	0.0% (0/40)
Chronic Kidney Disease	12.5% (5/40)
Current	10.0% (4/40)
Past, Resolved	2.5% (1/40)
Chronic Obstructive Pulmonary Disease	12.5% (5/40)

	Pivotal mITT Population N = 40
Current	12.5% (5/40)
Past, Resolved	0.0% (0/40)
Diabetes Requiring Insulin	22.5% (9/40)
Current	22.5% (9/40)
Past, Resolved	0.0% (0/40)
Diabetes Not Requiring Insulin	30.0% (12/40)
Current	30.0% (12/40)
Past, Resolved	0.0% (0/40)
Myocardial Infarction	10.0% (4/40)
Current	0.0% (0/40)
Past, Resolved	10.0% (4/40)
Peripheral Vascular Disease	2.5% (1/40)
Current	2.5% (1/40)
Past, Resolved	0.0% (0/40)
Pneumonia	5.0% (2/40)
Current	0.0% (0/40)
Past, Resolved	5.0% (2/40)
Psychiatry History	15.0% (6/40)
Current	15.0% (6/40)
Past, Resolved	0.0% (0/40)
Bladder Abnormalities	0.0% (0/40)
Current	0.0% (0/40)
Past, Resolved	0.0% (0/40)
Other medical history increasing infection risk	2.5% (1/40)
Current	2.5% (1/40)

	Pivotal mITT Population N = 40
Past, Resolved	0.0% (0/40)
Other	57.5% (23/40)
Current	52.5% (21/40)
Past, Resolved	5.0% (2/40)
Note: If patient has an entry for both current and past resolved for a category, they are presente d as current.	

Source Table 2.3

The most critical medical history for this product relates to the subjects' cirrhosis history. Details on the cirrhosis condition are shown in **Table 1**. The MELD-Na score was calculated using the method developed by Dr. Patrick S. Kamath [20] and Child Pugh score by C.G. Child [21]. The mean MELD-Na score was 15.2 ± 3.78 and mean Child Pugh score was 7.9 ± 0.97. The primary etiology for liver cirrhosis was alcohol (47.5%, 19/40) or non-alcoholic steatohepatitis (NASH) (37.5%, 15/40).

Table 18 Cirrhosis Condition details – Pivotal mITT

	Pivotal mITT Population N = 40
MELD-Na Score [1]	
Mean ± SD (N)	15.2 ± 3.78 (40)
Median (Min, Max)	16.0 (6.0, 25.0)
Child Pugh Score [1]	
Mean ± SD (N)	7.9 ± 0.97 (40)
Median (Min, Max)	8.0 (6.0, 11.0)
Etiology of Liver Disease [2]	
Alcohol	47.5% (19/40)
Non-alcoholic steatohepatitis (NASH)	37.5% (15/40)
Hepatitis C	10.0% (4/40)
Hepatitis B	2.5% (1/40)
Autoimmune Hepatitis	2.5% (1/40)

	Pivotal mITT Population N = 40
Primary Biliary Cirrhosis	0.0% (0/40)
Cryptogenic	7.5% (3/40)
Cardiac	0.0% (0/40)
Hemochromatosis	2.5% (1/40)
Drug-induced	0.0% (0/40)
Budd Chiari Syndrome	0.0% (0/40)
Other	15.0% (6/40)
[1] At time of enrollment. [2] Patient may have more than one etiology of liver disease identified so numbers sum to greater than 100%.	

Source Table 2.4.1

Baseline ascites and paracentesis history are shown in **Table 1.** The mean duration of refractory/recurrent ascites diagnosis was 15.7 ± 14.82 months (range including up to 64.8 months), with a mean number of 3.0 ± 1.33 paracenteses in the 1 month prior to baseline. The majority of patients had refractory ascites due to failure of diuretic therapy manifested by minimal to no weight loss coupled with inadequate Na excretion (62.5%, 25/40), with 15 patients having clinically significant complications of diuretics (37.5%, 15/40). Most patients were not candidates for liver transplant (72.5%, 29/40). None of the patients were candidates for TIPS: TIPS was contraindicated in 50.0% (20/40) of patients, TIPS was refused in 47.5% (19/40) of patients, one patient (2.5%) had previous TIPS implant closed, insufficient or obstructed and one patient (2.5%) had other reasons for no TIPS (Model of End-Stage Liver Disease (MELD) score too high). Note that there was one subject who had 2 reasons for no TIPS: refused and contraindicated.

Table 19 Baseline Ascites and Paracentesis History – Pivotal mITT

	Pivotal mITT Population N = 40
Duration of Refractory/Recurrent Ascites Diagnosis (months) [1]	
Mean ± SD (N)	15.7 ± 14.82 (40)
Median (Min, Max)	9.5 (0.7, 64.8)
Number of paracenteses in month prior	

	Pivotal mITT Population N = 40
Mean ± SD (N)	3.0 ± 1.33 (40)
Median (Min, Max)	3.0 (1.0, 7.0)
Ascites Type	
Minimal/no weight loss + inadequate Na excretion (Diuretic-Resistant)	62.5% (25/40)
Clinically significant complications of diuretics (Diuretic-Intractable)	37.5% (15/40)
Other	0.0% (0/40)
Liver transplant candidate	
Yes	20.0% (8/40)
No	72.5% (29/40)
Unknown	7.5% (3/40)
TIPS candidate [2]	
Yes	0.0% (0/40)
No, refused	47.5% (19/40)
No, contraindicated	50.0% (20/40)
No, other	2.5% (1/40)
N/A, previous implant closed, insufficient, obstructed	2.5% (1/40)
ECOG performance status	
0	5.0% (2/40)
1	37.5% (15/40)
2	42.5% (17/40)
3	15.0% (6/40)
4	0.0% (0/40)
5	0.0% (0/40)

[1] Month and year of diagnosis of refractory/recurrent ascites was collected. If month was missing it was assumed to be January.
[2] Patient may have more than one reason for not being a TIPS candidate so numbers may sum to greater than the total.

Source Table 2.5

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the pivotal cohort of 40 patients/procedures available for the 6-month evaluation. The key safety outcomes for this study are presented below in Tables 20 to 21. Adverse effects are reported in Table 22.

Safety events through the Primary Endpoint Period (6 months) are summarized in **Table 20.** The primary safety endpoint (PSE) is the combined rate of open surgical re-intervention (requiring general anesthesia or laparotomy) due to a pump system-related adverse event or to restore pump functionality, pump explant (without replacement) due to a pump system-related adverse event, or pump system-related death from time of pump implant through 6 months post-implant (as adjudicated by the CEC). The rate of PSEs was within the expected range for alfapump® implant and was similar to those reported for previous alfapump® studies [22-24]. It is further known that patients with advanced cirrhosis are at higher risk of complications after surgical procedures [25], which could be applied to the alfapump® implant. This is evidenced by the increase in peri-procedural events. As expected, the majority of PSE events were alfapump® explants due to a pump system-related AE, and included bacterial peritonitis, implant site erosion, wound dehiscence, bacterascites and bladder spasm. No deaths within 6 months of implant were related to the alfapump® device, therapy, or procedure in the pivotal cohort and only one roll-in subject had a death related to the alfapump®. The death occurred as a direct result of a technical complication during the implant procedure. This underscores the requirement for physician training on device placement and patient monitoring.

Secondary safety endpoints included review of re-interventions, Major Adverse Events (MAEs), device related infections, serious adverse events (SAEs) related to the device and evaluation of hepato-renal syndrome/acute kidney injury (HRS/AKI) events. Treatment was resumed successfully after revisions (non-explants). The pre-implant observation MAE rates were comparable to those reported in the post-implant observation period (7.5% vs 10%, respectively), underlining that the study includes a high-risk patient population. Device, procedure or therapy related infections were reported in 35% of patients through 6 months post alfapump® implantation. It is known that the patient population with refractory or recurrent ascites is more vulnerable to infections compared to patients without cirrhosis. This is related to numerous cirrhosis-specific factors, including severity of liver disease [26]. In addition, over half the studied population was diabetic, further increasing the risk of infection. The pre-implant observation period rate of infections was comparable to the post-implant observation period. The most commonly reported safety event was AKI. Of the events that were reported, the majority were Stage 1 (35.0%, 14/40). HRS/AKI events occurred mostly through 30 days following implantation and the majority resolved without sequelae. HRS/AKI stage 2 or higher events are more common in patients with lower baseline sodium.

Table 20 Overview Safety Outcomes Pivotal Cohort through the Primary Endpoint (6 months)

Endpoint	Summary	
Primary Safety Endpoint		
Primary Safety Endpoint	17.6% (95% CI: 6.76-34.53)	
Open Surgical Re-intervention	0%	
Pump Explant Without Replacement due to Related AE	17.6% (6.76-34.53), 6 events	
Pump System Related Death	0%	
Secondary Safety Endpoints		
Re-interventions	22.5% (9/40)	
	Pre-implant Observation Period	Post-implant Observation Period
MAES (AKI > stage 2, HRS, HE > stage 2, SBP or recurrent/refractory infection)	7.5% (3/40)	10% (4/40)
Serious Infection Events	5% (2/40)	7.5% (3/40)
Ascites Related Infections	2.5% (1/40)	5% (2/40)
Device, Therapy and Procedure related Infections	35% (14/40)	
Device, Therapy and Procedure related SAEs	55% (22/40)	
Any SAE	60% (24/40)	
Resulting in death (unrelated)	12.5% (5/40)	
Resulting in hospitalization	42.5% (17/40)	
Liver transplant	5% (2/40)	
Survival		
Freedom from death or explant related to alfapump	80.6%	
Overall survival	87.2%	
Transplant free survival	82.2%	
Patient survival on pump	64.9%	
Pump survival	75.2%	

The results beyond the Primary Endpoint analysis (>6 months), remained consistent with those reported for the first 6 months. No new safety signals were identified in the post-Primary Endpoint follow-up phase that raise concerns associated with the safety of the alfapump® System. The rates of mortality and adverse events are in line with expectations for this high-risk patient population and the mortality rate is consistent with the standard of care treatment with paracentesis or TIPS. There were two additional deaths that were adjudicated with the alfapump® being "contributory" to the death but with other patient factors noted to play a role. This highlights the critically ill status of these patients and the need to have diligent monitoring of them, especially with regard to their propensity for infection.

The reported safety events are not uncommon for this population with decompensated liver cirrhosis. Hepatic encephalopathy occurs in as many as 40% of patients with cirrhosis and is more common among those with portal hypertension and alcohol-related liver disease [27]. In a direct comparison between the alfapump® and LVP in an RCT, the rate of hepato-renal syndrome (HRS) was 30% in patients with alfapump® and 29% in the LVP arm. Similarly, the rate of infections was comparable between alfapump® and LVP (33% vs 26%). These rates are similar to rates reported in the current study and the frequency of reported MAEs aligns with those reported in the general patient population with decompensated liver cirrhosis. Furthermore, most of the MAEs occurred within the first months after alfapump® implant and occurred less frequently over time.

Complications related to AKI and infection were carefully studied in the POSEIDON trial. Most reported AKI events in the POSEIDON study were Stage 1 and would likely not have been identified had it not been for the frequent creatinine checks performed. This also allows for prompt treatment of these low-grade AKI events, potentially preventing progression to higher grades of AKI. Most AKI events were reported in the first months after the alfapump® implant and the frequency of AKI decreased over time. In both the pivotal and roll-in cohorts, there were minimal changes in mean estimated glomerular filtration rate (eGFR) over time, indicating no overall worsening in kidney function through 6 months post-implant. AKI is a well-known risk in patients with liver cirrhosis. It occurs in up to 50% of hospitalized patients with cirrhosis (Nadim et al., 2023).

Infection is a known and expected risk when introducing an implant in this at-risk patient population as they have generally increased susceptibility due to cirrhosis-related altered immunity [26]. Bacterial infections are present in approximately one-third of patients with cirrhosis who are hospitalized [3]. Risk mitigations in the current study included the use of prophylactic antibiotics and careful attention to wound care, as well as careful monitoring for any signs or symptoms of infection in implanted patients.

Reported mortality rates in the published literature for recurrent and refractory ascites vary and depend on multiple factors, such age, nutritional status, and medical comorbidities. A brief overview of reported mortality and survival rates

through 2-year follow-up in patients with ascites (as presented previously) in comparison to the POSEIDON trial results is shown in **Table 21.**

Table 21 Overview Mortality Rates from Published Literature

	Standard of Care	TIPS
Mortality 6 months	10.8 % (Bajaj et al.) * ***12.5% (POSEIDON Pivotal mITT)*** 13% (Bureau et al.)	
Mortality 12 months	22% (Macdonald, diuretic resistant) **25% *POSEIDON Pivotal mITT*** 29% ((Macdonald, diuretic intractable) 40% (EASL) 45% (Will) 46% (Tan, PICD-) 48% (Salerno) 50% (Tan, PICD+)	33% (Salerno et al.)
Mortality 24 months	***30% POSEIDON Pivotal mITT*** 37% (Larrue) 42% (Balcar) 50% (EASL) 59% (Tan, PICD-) 60% (Larrue, subgroup refractory ascites) 68% (Tan, PICD+) 71% (Salerno)	29% (Larrue) 39% (Larrue, subgroup refractory ascites) 41% (Salerno)
Abbreviations: PICD = Paracentesis-induced circulatory dysfunction; SOC =Standard of care; TIPS = Transjugular intrahepatic portosystemic shunt * Bajaj et al., Data on file.		

Reported mortality rates range up to 13% at 6 months to as much as 71% at 2 years with LVP. Depending on whether patients have high MELD scores or develop Paracentesis-induced circulatory dysfunction (PCID), survival prognosis is worse. In the matched cohort comparison (Bajaj et al.[2]), the mortality rate at 6 months was comparable to the rates reported in the POSEIDON pivotal cohort patients (10.8%). Also in a recent meta-analysis, survival in patients who underwent TIPS was reported to be 71% at 2 years and survival in patients who underwent paracentesis was 63% [28]. These rates were comparable to the survival rate observed for the POSEIDON pivotal cohort patients (61.5%) at 2 years following alfapump® implant. Survival rates for the subgroup with refractory ascites were much worse (up to 60% mortality at 2 years for LVP patients).

[2] Bajaj et al., Data on file.

Results from the literature indicate that the overall survival with the alfapump® was not worse as compared to TIPS and was higher than reported for standard of care (LVP). They further support that alfapump® implant did not adversely affect survival rates. Overall, the POSEIDON study has demonstrated an effective clinical outcome with a well characterized and acceptable safety profile.

The study results support the overall safety of the product and support a positive risk to benefit balance.

Adverse effects that occurred in the PMA clinical study:

An analysis of overall SAEs that occurred through 24 months post-implant for the Pivotal Cohort is included below. There were 110 SAEs reported in 29 patients (72.5%, 29/40, **Table 22**) through the 12 months and 148 SAEs in 32 patients through the 24-month (80%, 32/40) follow-up. Most SAEs were reported in the first months after alfapump® implantation (**Figure 3**).

The most commonly reported SAEs through 24 months were reported under the standard of care (SOC) infections and infestations (35.0%, 14/40), renal and urinary disorders (50%, 20/40), nervous system disorders (27.5%, 11/40) and gastrointestinal disorders (27.5%, 11/40). AKI was reported in 16 patients (40%, 16/40) through the 24-month follow-up. Between 0- and 24-months post-alfapump® implant, 12 fatal SAEs were reported. These were primarily unrelated to the alfapump® system.

Overall, SAEs reported in this study are commonly reported complications in patients with recurrent or refractory ascites and rates of events generally align with those reported in this overall patient population (i.e., 43% for PICD- patients and 51% for PICD plus patients) [29].

Table 22 Serious Adverse Events Through 24 Months – Pivotal mITT

	12 Months Post-Implant (Days 0 to Days 365)		24 Months Post-Implant (Days 0 to Days 730)	
	Number of Events N	**Patients with Events % (n/N)**	**Number of Events N**	**Patients with Events % (n/N)**
Total Number of SAEs	110	72.5% (29/40)	148	80.0% (32/40)
Number of SAEs Resulting in Hospitalization or Death	100	67.5% (27/40)	136	75.0% (30/40)

	12 Months Post-Implant (Days 0 to Days 365)		24 Months Post-Implant (Days 0 to Days 730)	
	Number of Events N	**Patients with Events % (n/N)**	**Number of Events N**	**Patients with Events % (n/N)**
Blood and lymphatic system disorders	2	5.0% (2/40)	3	5.0% (2/40)
Anaemia	2	5.0% (2/40)	2	5.0% (2/40)
Leukocytosis	0	0.0% (0/40)	1	2.5% (1/40)
Cardiac disorders	2	5.0% (2/40)	2	5.0% (2/40)
Atrial fibrillation	1	2.5% (1/40)	1	2.5% (1/40)
Cardiac arrest	1	2.5% (1/40)	1	2.5% (1/40)
Gastrointestinal disorders	14	20.0% (8/40)	20	27.5% (11/40)
Abdominal distension	1	2.5% (1/40)	1	2.5% (1/40)
Abdominal hernia	0	0.0% (0/40)	1	2.5% (1/40)
Abdominal pain	1	2.5% (1/40)	2	5.0% (2/40)
Abdominal pain upper	1	2.5% (1/40)	1	2.5% (1/40)
Abdominal wall haematoma	1	2.5% (1/40)	1	2.5% (1/40)
Gastrointestinal haemorrhage	3	7.5% (3/40)	5	7.5% (3/40)
Haemoperitoneum	1	2.5% (1/40)	1	2.5% (1/40)

	12 Months Post-Implant (Days 0 to Days 365)		24 Months Post-Implant (Days 0 to Days 730)	
	Number of Events N	**Patients with Events % (n/N)**	**Number of Events N**	**Patients with Events % (n/N)**
Ileus	3	5.0% (2/40)	3	5.0% (2/40)
Incarcerated umbilical hernia	1	2.5% (1/40)	1	2.5% (1/40)
Pancreatitis	1	2.5% (1/40)	1	2.5% (1/40)
Rectal haemorrhage	0	0.0% (0/40)	1	2.5% (1/40)
Upper gastrointestinal haemorrhage	1	2.5% (1/40)	2	5.0% (2/40)
General disorders and administration site conditions	8	17.5% (7/40)	11	20.0% (8/40)
Implant site erosion	3	7.5% (3/40)	4	10.0% (4/40)
Implant site extravasation	1	2.5% (1/40)	1	2.5% (1/40)
Implant site pain	0	0.0% (0/40)	1	2.5% (1/40)
Incarcerated hernia	1	2.5% (1/40)	1	2.5% (1/40)
Multiple organ dysfunction syndrome	1	2.5% (1/40)	1	2.5% (1/40)
Pyrexia	1	2.5% (1/40)	2	5.0% (2/40)
Treatment noncompliance	1	2.5% (1/40)	1	2.5% (1/40)
Hepatobiliary disorders	4	10.0% (4/40)	7	17.5% (7/40)

	12 Months Post-Implant (Days 0 to Days 365)		24 Months Post-Implant (Days 0 to Days 730)	
	Number of Events N	**Patients with Events % (n/N)**	**Number of Events N**	**Patients with Events % (n/N)**
Hepatic failure	2	5.0% (2/40)	5	12.5% (5/40)
Hepatorenal syndrome	2	5.0% (2/40)	2	5.0% (2/40)
Immune system disorders	0	0.0% (0/40)	1	2.5% (1/40)
Drug hypersensitivity	0	0.0% (0/40)	1	2.5% (1/40)
Infections and infestations	19	32.5% (13/40)	24	35.0% (14/40)
Anal abscess	1	2.5% (1/40)	1	2.5% (1/40)
Bacteraemia	1	2.5% (1/40)	2	5.0% (2/40)
Bacterascites	3	7.5% (3/40)	5	7.5% (3/40)
COVID-19	2	5.0% (2/40)	2	5.0% (2/40)
COVID-19 pneumonia	2	5.0% (2/40)	2	5.0% (2/40)
Implant site cellulitis	1	2.5% (1/40)	1	2.5% (1/40)
Peritonitis bacterial	5	12.5% (5/40)	6	12.5% (5/40)
Pneumonia	1	2.5% (1/40)	1	2.5% (1/40)
Sepsis	1	2.5% (1/40)	2	5.0% (2/40)

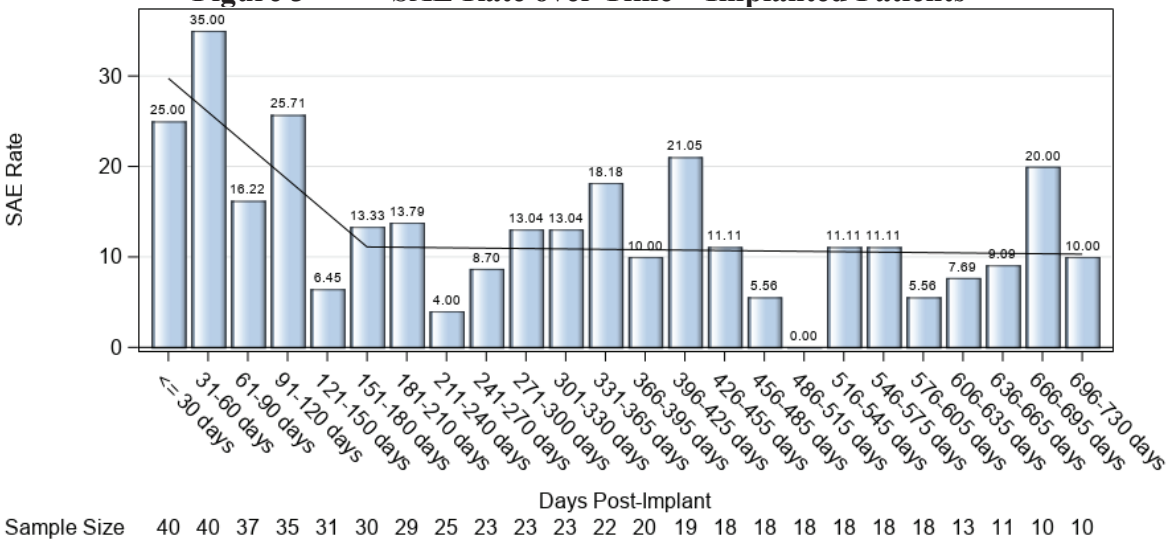
	12 Months Post-Implant (Days 0 to Days 365)		24 Months Post-Implant (Days 0 to Days 730)	
	Number of Events N	**Patients with Events % (n/N)**	**Number of Events N**	**Patients with Events % (n/N)**
Urinary tract infection	2	5.0% (2/40)	2	5.0% (2/40)
Injury, poisoning and procedural complications	8	12.5% (5/40)	8	12.5% (5/40)
Device placement issue	1	2.5% (1/40)	1	2.5% (1/40)
Fall	1	2.5% (1/40)	1	2.5% (1/40)
Procedural pneumothorax	1	2.5% (1/40)	1	2.5% (1/40)
Transplant rejection	1	2.5% (1/40)	1	2.5% (1/40)
Wound dehiscence	4	5.0% (2/40)	4	5.0% (2/40)
Metabolism and nutrition disorders	8	12.5% (5/40)	12	20.0% (8/40)
Acidosis	0	0.0% (0/40)	1	2.5% (1/40)
Electrolyte imbalance	2	2.5% (1/40)	2	2.5% (1/40)
Hyperglycaemia	1	2.5% (1/40)	1	2.5% (1/40)
Hyperkalaemia	4	7.5% (3/40)	5	10.0% (4/40)
Hyponatraemia	0	0.0% (0/40)	2	2.5% (1/40)
Hypovolaemia	1	2.5% (1/40)	1	2.5% (1/40)

	12 Months Post-Implant (Days 0 to Days 365)		24 Months Post-Implant (Days 0 to Days 730)	
	Number of Events N	**Patients with Events % (n/N)**	**Number of Events N**	**Patients with Events % (n/N)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	2.5% (1/40)	1	2.5% (1/40)
Hepatic neoplasm	1	2.5% (1/40)	1	2.5% (1/40)
Nervous system disorders	15	25.0% (10/40)	19	27.5% (11/40)
Hepatic encephalopathy	15	25.0% (10/40)	19	27.5% (11/40)
Product issues	1	2.5% (1/40)	2	5.0% (2/40)
Device dislocation	1	2.5% (1/40)	1	2.5% (1/40)
Device malfunction	0	0.0% (0/40)	1	2.5% (1/40)
Psychiatric disorders	1	2.5% (1/40)	1	2.5% (1/40)
Mental status changes	1	2.5% (1/40)	1	2.5% (1/40)
Renal and urinary disorders	23	45.0% (18/40)	33	50.0% (20/40)
Acute kidney injury	16	35.0% (14/40)	26	40.0% (16/40)
Bladder spasm	4	10.0% (4/40)	4	10.0% (4/40)
Haematuria	2	5.0% (2/40)	2	5.0% (2/40)
Urinary retention	1	2.5% (1/40)	1	2.5% (1/40)

	12 Months Post-Implant (Days 0 to Days 365)		24 Months Post-Implant (Days 0 to Days 730)	
	Number of Events N	**Patients with Events % (n/N)**	**Number of Events N**	**Patients with Events % (n/N)**
Respiratory, thoracic and mediastinal disorders	3	7.5% (3/40)	3	7.5% (3/40)
Aspiration	1	2.5% (1/40)	1	2.5% (1/40)
Respiratory failure	2	5.0% (2/40)	2	5.0% (2/40)
Vascular disorders	1	2.5% (1/40)	1	2.5% (1/40)
Hypotension	1	2.5% (1/40)	1	2.5% (1/40)
Note: All events that occurred while the patient was active in the study are included. Note: 1 Serious adverse events occurred after day 730 but prior to study exit among patients who did not participate in the optional long-term follow-up. These events are included in the 24-month analysis.				

Source Table 7.6.1

Figure 3 SAE Rate over Time – Implanted Patients



Sample Size	40	40	37	35	31	30	29	25	23	23	23	22	20	19	18	18	18	18	18	18	13	11	10	10

Note: The numerator is the number of patients with at least one SAE in the time period of interest. The denominator is the number of patients still enrolled in the study for at least a portion of the time period of interest.

Note: 1 patient who did not participate in the optional long term follow-up experienced events after day 730 but prior to study exit. These events are included in the calculation for the 696-730 days column.

Percentage is number of subjects with at least one SAE in window divided by number of patients enrolled in study.

2. Effectiveness Results

The analysis of effectiveness was based on the 40 evaluable patients at the 6-month time point. Key effectiveness outcomes are presented in Tables 22-24.

The alfapump® System is intended to provide a more effective treatment option for patients with refractory or recurrent ascites due to liver cirrhosis. As noted previously, the class of patients intended to receive treatment with the alfapump® currently undergo the standard of care treatment of LVP, which although effective, has its challenges, both psychosocial and physical. The alfapump® System is designed to reduce or eliminate the need for therapeutic paracentesis, and to thereby improve subjective physical health and ascites symptoms.

The POSEIDON study examined both technical endpoints and quality of life/general wellbeing endpoints. The results demonstrate a significant reduction in therapeutic paracentesis, elimination of the need for therapeutic paracentesis in the majority of patients (73.1%) and a highly significant reduction in the average monthly number of therapeutic paracenteses compared to pre-implant with a significant p value of <0.001. These technical outcomes are consistent with previous studies using the alfapump [22-24].

Table 23 summarizes the co-primary effectiveness endpoints. These results were maintained during the long-term follow-up (beyond 6 months), with 60.5% of patients being freed from therapeutic paracentesis at 24 months.

Table 23 Co-Primary Effectiveness Pivotal Cohort through the Primary Endpoint Period (6 months)

Endpoint	Performance Goal	POSEIDON Study Result	Statistical Significance
Reduction in Median Number of Therapeutic Paracentesis / Month	50% reduction	100% reduction	**p<0.001**
% of Patients with 50% reduction therapeutic paracentesis	50% of patients	77% of patients	**p<0.001**

Given that the median 1-year mortality in patients with refractory ascites is reported to be as high as 48% [4, 30], quality of life is key in the alfapump® performance. **Table 24** presents the outcomes for the quality-of-life measures studied in the POSEIDON trial.

The FDA determines the POSEIDON study successfully met both co-primary effectiveness endpoints and supports use of the pump for refractory or recurrent ascites in end-stage liver disease patients as there is clinical benefit. The mortality and adverse events rates are in line with expectations for this high-risk patient population, and the mortality rate is consistent with standard of care treatment.

Of particular note is the statistically significant improvement in AscitesQ- (P<0.001) [3], and the clinically and statistically significant improvement in SF-36 Physical Component T-Score (P<0.001), with the observed average change exceeding the recommended minimum clinically important difference of 2 T-Score points in the SF-36 user manual [35]. Additionally, the user manual recommends defining a responder on the SF-36 PCS as a subject with an improvement of at least 3.8 T-score points. Based on this criterion, 61.5% of subjects had a clinically meaningful improvement in SF-36 PCS T-Score. These outcomes are consistent with results reported in earlier studies using the alfapump® [31].

[3] While statistically significant, this change may not be clinically significant

Table 24 Summary POSEIDON Study Patient Reported Outcome Secondary Endpoint Data through 6 months

Quality of Life Item	Change	Statistical Significance†
SF-36 Physical Component Summary T-Score	Improved by average of 6.4 T-Score points (exceeds clinically important difference of 2T-score points) 61.5% of patients were responders as defined by a clinically meaningful improvement (T-score change of at least 3.8 T-score points)	**p<0.001**
Ascites-Q score	Improved by 16.8 points*	**p<0.001***

†Comparison of pre implant to 6 month outcome
*this difference while statistically significant, may not be clinically meaningful

A summary of effectiveness outcomes through 24 months are shown in the **Table 25.**

Table 25 Summary of Cumulative Effectiveness Data Through 24 Months – Pivotal mITT*

Endpoint	Data from 0 to 6 months	Data from 0 to 12 Months	Data from 0 to 24 Months
Freedom from therapeutic paracentesis (>1.5L)	73% of patients	65% of patients	61% of patients
Freedom from LVP	90% of patients	86% of patients	80%
Number of therapeutic paracentesis procedures per month	Median of 0.0	Median of 0.0	Median of 0.0
Average volume of ascitic fluid removed with therapeutic paracentesis	Less than 1L	Less than 1L	Less than 3L
Percentage of total volume of ascitic fluid removed by the alfapump	97%	99%	87%
Evolution of renal function as assessed by eGFR	-2.5 mL/min/1.73m^2	-5.4 mL/min/1.73m^2	-6.6 mL/min/1.73m^2
Nutritional status as assessed by PSOAS Score	N/A	+3.5 cm^2/m^2	+ 1.4 cm^2/m^2
Evolution of Prealbumin values	+ 2.4 mg/dL to above critical threshold level of 10 mg/dL	+ 2.8 mg/dL to above critical threshold level of 10 mg/dL	+ 1.8 mg/dL to above critical threshold level of 10 mg/dL
Evolution of MELD-Na score	+0.8 points	+ 1.7 points	+ 2.2 points
Change in SF-36 Score PCS and MCS	+ 6.4 points in PCS +3.1 points in MCS	+ 5.1 points in PCS + 1.9 points in MCS	+ 9.3 points in PCS + 7.0 points in MCS
Change in Ascites-Q Score	-16.8 points	-14.7 points	-26.6 points
Abdominal distension satisfaction	77% of patients with increase by 1 level or more on the scale	83% of patients with increase by 1 level or more on the scale	100% of patients with increase by 1 level or more on the scale
Proportion of days where the patient reported satisfaction with the size of their abdomen	+ 11 additional days satisfied with abdomen	No Diary Data Collected	No Diary Data Collected
Proportion of days where the patient reports a positive global assessment of health	+ 10 Good Health Days	No Diary Data Collected	No Diary Data Collected

*This study was not designed to assess statistical or clinical significance of study endpoints other than those cited to be specifically intended for labeling claim (Tables 9 and 10).

3. Subgroup Analyses
   Sub-group analyses were conducted for age, gender, race, ethnicity, and number of paracenteses in the month prior to implant. There were no significant effects seen in any of these sub-group analyses on primary effectiveness or safety endpoints for the trial. The study was not specifically powered for age, gender, race, ethnicity, or number of paracenteses subgroups.

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. 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. The pivotal clinical study included 143 investigators. None of the study investigators were a fulltime or part-time employee of the sponsor, and therefore, have provided sufficient accurate financial information to allow for compete disclosure or certification as required under 21 CFR 54.4. There were no sites where investigators had a disclosable financial interest in Sequana Medical.

XII. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

To further enhance the body of scientific evidence for the use of the alfapump® System additional data sources were obtained which included:

1. Patient Preference
   A Patient Preference study was completed by RTI Health Solutions (RTI-HS) to characterize the level of risk patients are willing to accept as a consequence of a treatment with an implantable pump for liver ascites. The Patient Preference study utilized the discrete-choice experiment (DCE) method to elicit preferences for attributes of an implantable pump among patients with ascites. The study was collaboratively designed with input from the FDA, incorporating FDA's feedback on the survey design.

   The study data confirm that patients with recurrent or refractory ascites are interested in alternative treatment options. Patients indicated that they were willing to tolerate risks beyond what has been observed in the POSEIDON clinical experience to reduce the need for therapeutic paracentesis (**Table 26**).

   The probability of respondents selecting the alfapump® profile (aligned with the POSEIDON trial outcomes) over continuing their current paracentesis schedule was calculated. The model predicts a 63.5% probability that respondents would choose a pump profile similar to the alfapump®.

Table 26 Overview of Patient Preference Results

	Patient Preference Study Maximum Acceptable Risk*	Observed Rate in POSEIDON
Major surgery or death	>10%	0%
Minor procedure	>35%	20%
Serious infection or AKI requiring hospitalization	>30%	22.5%

* with other attributes as reported in the Poseidon trial

In summary, the patient preference study data supports that the alfapump® would be a desirable option for a majority of patients with recurrent and refractory ascites.

2. NACSELD III

The North American Consortium for the Study of End Stage Liver Disease (NACSELD III registry study, funded by Sequana Medical, included matched 1:1 matched analysis of 40 patients in the POSEIDON Pivotal Cohort with the registry patients. Matched patients from the POSEIDON cohort and the NACSELD III registry showed similar rates of mortality and slightly higher rates of hospitalization for POSEIDON patients, indicating that mortality rate following placement of the alfapump is not worse than mortality for standard paracentesis over 6 months and slightly higher hospitalization rates in the first 6 months post-implant that reflect the added risk the surgical procedure for placement of the alfapump® (**Table 27**).

Table 27 6-Month Outcomes in Registry Matched Subjects vs POSEIDON Pivotal Cohort

	POSEIDON Pivotal Cohort (N = 37)	Registry Matched Patients (N = 37)
Any SAE Resulting in Death or Requiring Hospitalization	56.8% (21/37)	45.9% (17/37)
Deaths	10.8% (4/37)	10.8% (4/37)
SAE Requiring Hospitalization	45.9% (17/37)	35.1% (13/37)
Median # of hospitalizations (Min, Max)	1 (0, 4)	0 (0, 4)
Transplants	5.4% (2/37)	8.1% (3/40)
Note: Deaths and SAE Requiring Hospitalization are presented hierarchically such that if a subject died and experienced an SAE requiring hospitalization, they are counted in the Death row.		

This comparison provides further context for safety and mortality results, given that rapid disease progression in this patient population limits the utility of the pre-implant observation period as the sole comparator for these outcomes.

3. Real World Evidence (RWE) from Medicare SAF

Data from POSEIDON patients were compared with real world evidence using data extracted from the 2017-2019 Medicare Inpatient & Outpatient Hospital SAFs containing inpatient & outpatient hospital claims for 100% of Medicare claims processed by CMS[4]. Data was extracted from 2017-2020 to avoid use of data during the COVID pandemic and included only patients 65 and older. A total of 701 patients with refractory ascites were identified. Mortality rate through 2 years was comparable to the mortality rates reported for the Pivotal POSEIDON patients who were 65 or older, indicating that implant with the alfapump® did not lead to increased mortality rates in this patient population. In addition, in-patient hospitalizations in patients 65 and older were not increased with the alfapump® implant as compared to real world data from the Medicare SAF database **Table 28.**

[4] Medicare Inpatient & Outpatient Hospital Standard Analytical Files 2017-2019. Center for Medicare & Medicaid Services (CMS), Baltimore, MD. www.cms.hhs.gov

Table 28 Overview of Outcomes from the Medicare SAF Database

	6 Months Post		12 Months Post		24 Months Post	
	Medicare SAF (N-701)	**POSEIDON (n=19)**	**Medicare SAF (N-701)**	**POSEIDON (n=19)**	**Medicare SAF (N-701)**	**POSEIDON (n=19)**
Cumulative Percent Mortality (Deaths/total patients)	14.8%	15.8%	25.5%	26.3%	43.4%	36.8%
Cumulative % Patients with an Inpatient Hospitalization	68.9%	52.5%	82.2%	63.2%	88.7%	78.9%
Hospitalizations (Avg Number per patient)	1.7	1.0	2.6	1.4	3.3	1.8

4. Summary of Data from Prior alfapump Studies

Data from earlier studies on the alfapump® were reviewed to evaluate the safety and effectiveness of the alfapump®, considering the POSEIDON study data. Results from earlier alfapump® studies showed that the alfapump® significantly reduced the need for therapeutic paracentesis and LVP while improving quality of life, similar to what was observed for the POSEIDON data. Safety results from POSEIDON suggest treatment with the alfapump® has improved over time with respect to rates of reintervention and AKI due to improvements in the technology and in patient management. A summary of key outcomes across the prior studies (N=309 patients implanted) is tabulated below in Table 29 relative to POSEIDON trial results.

Table 29 Summary of alfapump® data vs POSEIDON Pivotal

	Through 6 months	**Through 12 months**	**Through 24 months**
Freedom from paracentesis	43% (Will) 40% (Bellot) ***73.1% POSEIDON Pivotal mITT***	~50% (MOSAIC) ***65.1% POSEIDON Pivotal mITT***	~30% (MOSAIC) ***60.5% POSEIDON Pivotal mITT***
Ascites Q Score Decrease	~16 (Wong, 2020) ***16.8 POSEIDON Pivotal mITT*** 19.6 (MOSAIC)	~11 (Wong , 2020) 14.5 (MOSAIC) **14.7** ***POSEIDON Pivotal mITT***	**26.4** ***POSEIDON Pivotal mITT***
Explant (excluding Liver Transplant and no longer needed)	**17.5%** ***POSEIDON Pivotal mITT*** 11.1% (Bureau)	***22.5% POSEIDON Pivotal mITT***	40% (MOSAIC) **35%** ***POSEIDON Pivotal mITT*** 30.4% (Stirnimann 2017) 21.7% (Stirnimann 2022)
Survival	~58% (Stirnimann 2022) ~61% (Stirnimann 2017) ~77% (Bureau) ~78% (MOSAIC) **87.2%** ***POSEIDON Pivotal mITT***	~44% (Stirnimann 2017) ~58% (MOSAIC) ~50% (Stirnimann 2022) **71.1%** ***POSEIDON Pivotal mITT***	~30% (Stirnimann 2017) ~30% (Stirnimann 2022) **61.5%** ***POSEIDON Pivotal mITT***
Any SAE	85.2% (Bureau) **60%** ***POSEIDON Pivotal mITT***	76.7% (MOSAIC) **72.5%** ***POSEIDON Pivotal mITT***	**80%** ***POSEIDON Pivotal mITT***

The totality of data amassed with the alfapump® for treatment of recurrent or refractory ascites in patients with liver cirrhosis support the safety and effectiveness results for the product with consistent results across these trials and demonstration

of some improvement in both safety and effectiveness profiles with advancements in the technology and patient management.

In summary, the scientific body of evidence to support the benefit-risk analysis for the alfapump® System support the results from the POSEIDON trial. When compared to a matched cohort from NACSELD III or the Medicare database, as well as rates reported in the literature, the mortality rate and overall rate of safety events were similar to those reported for patients managed using standard of care for recurrent and refractory ascites. Given the high mortality rate and comorbidities in this very sick patient population, implant with the alfapump® did not affect the survival.

XIII. 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 Gastroenterology-Urology Devices Panel (GUDP) FDA advisory committee.

XIV. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The Primary Effectiveness Endpoint for the POSEIDON trial was successfully achieved, demonstrating a significant reduction in therapeutic paracentesis, and elimination of the need of therapeutic paracentesis in the majority of patients through 6 months. In addition, a significant reduction in the frequency of average monthly LVP compared to pre-implant was demonstrated. These results from the current study are supported by results from previous studies using the alfapump® [22-24] for which the alfapump® is consistently reported to provide a reduction in frequency of paracentesis. In each of these studies, the alfapump® was demonstrated to function as intended (minimize accumulation of ascitic fluid in the abdominal cavity) and to be an effective approach for the management of ascites. Furthermore, in comparison to paracentesis, continuous removal of fluid using the alfapump® does not result in tense ascites re-accumulation, which causes discomfort and other physical challenges, over the course of treatment.

Overall, results from the current study demonstrate that alfapump® implant led to a meaningful reduction in therapeutic paracentesis that is sustained for the duration of time the alfapump® is implanted. The patient preference study conducted supports that patients value the benefit of reduction in frequency of paracentesis and will make significant risk tradeoffs for 50% or higher reduction in the frequency of paracentesis.

The Secondary Endpoints intended for Label Claim were also achieved, indicating an improvement in subjective physical health and ascites symptoms through the Primary Endpoint of 6 months post-implant [34]. The statistically significant improvement of 16.8 points in Ascites-Q score is similar to Ascites-Q outcomes as reported in earlier studies using the alfapump [31]. However, while this change is statistically significant and

consistent with declines reported for other studies, it might not be clinically meaningful. Improvement in the SF-36 Physical Component Summary (PCS) T-Score also saw both a clinically and statistically significant increase through the Primary Endpoint. The mean improvement of 6.4 T-Score points seen in SF-36 PCS T-Score exceeded the Minimal Clinically Important Difference (MCID) of 2 T-Score Points as defined by the SF-36 user manual [35]. Additionally, 61.5% of patients treated had an improvement in SF-36 PCS score of at least 3.8 T-Score points (defined by the SF-36 user manual as a clinically meaningful difference for defining a patient as a responder).

Furthermore, while baseline quality of life assessments indicated a deteriorated state of quality of life in this patient population, patients reported an increase of 10 days per month in which they felt their global health relative to their ascites symptoms and management was good, very good, or excellent (i.e. Ascites Good Health Days). The conducted patient preference study concluded that patients were willing to accept significant levels of risk for a pump that confers 10 additional Ascites Good Health Days.

Clinical evidence on the alfapump® demonstrate a consistently reported improvement in subjective physical health and ascites symptoms through 6 months in this patient population in which quality of life is expected to continue to decrease over time. The reduction in therapeutic paracentesis and continuous flow of ascites removal, helps avoid tense ascites and associated symptoms.

B. Safety Conclusions

Risks with the implant procedure and initial post implant period (through 6 months) have been well characterized by the POSEIDON trial, as well as with prior alfapump® studies conducted in the US and Europe and reported in the literature.

The primary risks within the peri-implant period include risk of explant due to poor tolerance of the device (implant site erosion or bladder discomfort), as well as the risk of AKI or infection due to the alfapump® resulting in the need for hospitalization. Patient acceptance of these risks has been confirmed by the patient preference study conducted by the sponsor that demonstrates that the risk of a minor procedure (e.g. explant or revision) and risk of hospitalization for AKI or infection that is acceptable to patients well exceeds the rates observed in the POSEIDON clinical study. Patients are willing to accept greater than a 35% risk of a minor procedure (vs. 20% POSEIDON) and > 30% risk of serious AKI or infection requiring hospitalization (vs. 22.5% in POSEIDON) over 6 months to receive the benefits of the alfapump® over continuing with paracentesis. Given the high degree of impact on quality of life in these patients, significant risk is acceptable for a treatment that offers reduction in paracentesis and the promise of better quality of life.

Regarding the overall SAE rates within 6 months post-implant of the alfapump®, the observed rates in the POSEIDON trial are comparable to the similar period pre-implant and to the randomized controlled trial (RCT) conducted by Bureau at al. RWE using the Medicare SAF data also support an equal or lower rate of hospitalization over a 6-month period. In addition, a matched comparison was performed comparing hospitalization rates

for NACSELD III-matched patients to POSEIDON patients. This matched comparison showed that the observed rate of hospitalization was slightly higher in POSEIDON patients (~10% within 6 months); however this difference did not reach statistical significance. Given the fact that POSEIDON patients undergo an operative procedure to implant the pump, a slightly higher rate of hospitalization within the first 6 months post-implant could be reasonably expected. In the POSEIDON trial, the rate of SAEs over time was noted to be high for the first few months, after which a steady rate of SAEs was observed. SAEs and hospitalization within 6 months post-implant may be slightly higher than the rate expected per Standard of Care paracentesis, but this increase is acceptable to patients and stabilizes after the initial post-implant period. SAE rates have improved over the entire course of alfapump® usage in this indication based on comparison of POSEIDON trial results and the alfapump® arm in the RCT by Bureau et al.

Mortality within 6 months post-implant is in line with all sources of data on this patient population. Literature mortality rates within 6 months for patients undergoing regular paracentesis are equal to or lower than those observed in the POSEIDON trial. The NACSELD III-matched control patients had an equal mortality rate. RWE data from Medicare SAF suggest mortality in patients 65 or older is equal to mortality observed in similar age patients in the POSEIDON trial. The risk of mortality related to the alfapump® or procedure is low. A single case of death within 6 months which was due to the implant procedure was observed in a roll-in cohort patient. Further mitigations were put in place after this to ensure heightened observation of patients post-implant and improved communication with primary care and referring physicians.

Risks associated with the long-term use of the alfapump® (> 6 months) have also been well characterized by the POSEIDON trial, as well as with prior alfapump® studies conducted in the US and Europe. The primary risks occurring with use of the alfapump® after 6 months include risk of explant due to infection and/or AKI and risk of death associated with these complications. Patient acceptance of these risks has also been confirmed by the patient preference study conducted by the sponsor that demonstrates that the risk of minor procedure (e.g. explant or revision) and risk of hospitalization for AKI or infection that is acceptable to patients well exceeds the rates observed in the POSEIDON clinical study. Given the high degree of impact on quality of life in these patients, significant risk is acceptable for a treatment that offers reduction in paracentesis and the promise of improvement in subjective physical health and ascites symptoms.

Regarding the overall SAE rates through 24 months post-implant of the alfapump®, the observed rates in the POSEIDON trial are equal or lower than the RWE using Medicare SAF data. SAEs and hospitalization through 24 months post-implant are within the expected range based on the available literature. This rate is acceptable to patients. The highest frequency of events related to the alfapump® were either AKI or infection. These events are managed by turning the pump down or off, giving albumin, intravenous (IV) antibiotics and ultimately, if needed, with explant.

Regarding the risk of AKI, most reported AKI events were minor events (stage 1) and resolved without sequelae. It should be noted that surveillance for AKI utilized a

conservative approach requiring frequent checks of creatinine. This frequent surveillance was much more likely to identify asymptomatic creatinine rises meeting the AKI stage 1 criteria. Based on literature, AKI events are common in this patient population, and AKI has been reported to vary from 14-50% in patients with decompensated cirrhosis, with AKI being higher post-surgical intervention in this patient population [37]. Further, no effect on overall survival was seen despite the AKI events related to alfapump® therapy. Mitigations that were put into place were not demonstrated to have an effect on the rate of AKI within the first 6 months post-implant. A predictors analysis did show low baseline sodium was predictive of stage 2-3 AKI and/or HRS Type I and that high creatinine and a history of urinary track infection (UTI) was predictive for any AKI event through 12 months (DMC, Risk Predictor Analysis, 09 May 2023).

Mortality through 24 months post implant is very much in line with all sources of data on this patient population. Literature mortality rates through 12 and 24 months for patients undergoing regular paracentesis are equal to or lower than those observed in the POSEIDON trial. RWE data from the Medicare SAF database suggest mortality in patients 65 or older is equal to mortality observed in similar age patients in the POSEIDON trial. The risk of mortality related to the alfapump® is low. Mitigations were put in place to reduce the risk of AKI and infection post-implant.

Patient acceptance of risks

The patient preference study conducted evaluated the maximum acceptable risk that patients were willing to accept for a device such as the alfapump®. The results of this study suggest that, on average, patients are willing to accept risks far greater than the levels observed in the POSEIDON trial. Respondents were willing to accept a >10% risk of major surgery or death, a >35% risk of a minor procedure, and a >30% risk of serious infection or AKI requiring hospitalization within 6 months to receive an implanted pump that reduced the frequency of paracentesis procedures by 100% and conferred 10 additional Ascites Good Health Days over no implanted pump. The average probability for selecting an alfapump®-like profile compared with selecting no new pump was 63.5%, further confirming that a majority of patients would accept the risks observed in the POSEIDON trial for an alfapump®. This preference for a pump over traditional paracentesis was consistent at 12 months in this survey.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Patients with recurrent or refractory ascites have limited treatment options available [38]. Many patients do not have good treatment options available to manage the ascites and consequently optimize quality of life as their disease progresses, beyond repeated paracentesis. As highlighted in this PMA Application, paracentesis as a management strategy is associated with poor quality of life in patients who are experiencing high morbidity and mortality due to their underlying disease. The cycle of paracentesis results in a high proportion of days with disruption to undergo regular paracentesis or with debilitating symptoms of tense ascites

between treatments which limits the days for which meaningful quality of life is possible [39].

The alfapump® offers patients an opportunity to experience the feeling of controlled ascitic fluid removal on a consistent basis. This results in drastic reduction or potentially complete elimination of the need for paracentesis. As a result, patients are provided with an improvement in subjective physical health and ascites symptoms. These benefits are meaningful to patients, as confirmed in the Patient Preference study. In the POSEIDON study, patients experienced a statistically and clinically significant improvement in subjective physical health as measured by SF-36 Physical Component Summary T-Score and a statistically significant improvement (which may not be clinically significant) in ascites symptoms as measured by the ASCITES-Q Questionnaire at 6-months post implant. These findings are supported by prior studies conducted with the alfapump®. Overall, the alfapump® System offers a feasible treatment option for cirrhotic patients. The device provides relief from the need for frequent paracentesis and eliminates the buildup of ascites fluid, allowing for improvement in subjective physical health and ascites symptoms.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Although alfapump® implant is not without risks, the risks associated with the use of the alfapump® have been well characterized in the POSEIDON trial, as well as with prior experience with the alfapump® in Europe. The alfapump® risks observed are consistent in type to those identified in this population without a pump. The frequency of serious adverse events requiring hospitalization may be elevated in the post-implant period due to the surgical procedure; however, the rate of mortality has been shown to be no worse for patients with alfapump® when compared to TIPS and paracentesis based on review of the literature, the matched NACSELD III registry, and RWE obtained using the Medicare SAF. In addition, the results of the Patient Preference study confirm that patients are willing to accept levels of risk that are higher than those observed in the POSEIDON trial to obtain the benefits conferred by the alfapump®.

Additional factors to be considered in determining probable risks and benefits for the alfapump® System included quality of life and patient perspectives. The importance of quality of life in the determination of benefit-risk is acknowledged by FDA in the guidance on Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval, noting that patient perspectives are important in benefit-risk assessments, specifically that "patient perspectives on benefits and risks may reveal reasonable patients who are willing to tolerate a very high level of risk to achieve a probable benefit, especially if that benefit results in an improvement in quality of life."[40] For the alfapump®, it has been demonstrated that this breakthrough technology addresses an unmet need by relieving the patient from the requirement of having to undergo frequent paracenteses and providing improvements in subjective physical health and ascites symptoms with risks that a majority of patients have conveyed are acceptable. The data included in this application support the overall safety of the product and support a positive risk to benefit balance.

1. Patient Perspective

   Patient perspectives considered during the review included information on how a patient feels or functions as reported using the Ascites-Q, a measure of Ascites symptoms, and the SF-36 PCS, a measure of subjective physical health. In the POSIDEON pivotal clinical study, change in both of these scores from baseline to 6-months were secondary effectiveness endpoints. These findings are summarized in Table 10. From baseline to 6 months, participants improved by an average of 6.4 T-score points on the SF-36 PCS; this was a statistically and clinically meaningful improvement in subjective physical health. Participants improve by 16.8 points on the Ascites-Q; while this was statistically significant, it may not be clinically meaningful. In summary, patient-reported outcome findings found a benefit, as participants implanted with the product experienced a meaningful improvement in subjective physical health and potentially meaningful improvement in ascites symptoms.

   Another way that patient perspectives were considered during the review is through a patient preference information study. A study of 125 respondents with cirrhotic liver disease managed primarily with therapeutic paracentesis completed a stated preference survey. The study, which used candidates for an alfapump®, concluded that, on average, patients are willing to accept levels of risks associated with the alfapump® (e.g. death, major/minor surgical procedure, or infection or kidney injury requiring hospitalization) far greater than the rates observed in the POSEIDON trial to receive an alfapump® that reduces the need for paracentesis over continuing with regular paracentesis.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

A compilation of a compendium of valid scientific evidence regarding the alfapump® performance and a comparison of the product performance in reference to the current clinical options for the indicated patient population intended for the product is provided to support a benefit-risk analysis. The evidence includes the clinical trial results from POSEIDON and results from prospective clinical trials with the alfapump® performed world-wide, as well as a patient preference study, clinical registries on consistent patient populations, Medicare evidence on outcomes for the indicated patient population and evidence on the standard of care from the literature. A robust analysis has indicated that the benefits of the alfapump® outweigh the attendant risks of this product and therapy.

XV. CDRH DECISION

CDRH issued an approval order on December 20, 2024

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

XVI. 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: N/A ~~See approval order.~~

XVII. REFERENCES

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