SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name:	Selective Cytopheretic Device
Device Trade Name:	QUELIMMUNE
Device Procode:	QZV
Applicant's Name and Address:	SeaStar Medical, Inc. 3513 Brighton Blvd, Ste 410 Denver, CO 80216
Humanitarian Device Exemption (HDE) Number:	BH220740
Humanitarian Use Device (HUD) Designation Number:	DEV-2019-434
Date of Panel Recommendation:	N/A
Date of HUD Designation:	June 10, 2020
Date of Notice of Approval to the Applicant:	February 21, 2024

II. INDICATIONS FOR USE

HUMANITARIAN DEVICE: Authorized by Federal law for use in the treatment of pediatric patients ≥10kg with acute kidney injury due to sepsis or a septic condition requiring renal replacement therapy. The effectiveness of this device for this use has not been demonstrated.

The Selective Cytopheretic Device for Pediatrics (SCD-PED) is indicated for treatment of pediatric patients (weight ≥10kg and age ≤22 years) with acute kidney injury (AKI) due to sepsis or a septic condition on antibiotic therapy and requiring renal replacement therapy (RRT).

III. CONTRAINDICATIONS

Use of the SCD-PED as a stand-alone unit to provide any renal replacement therapy or fluid and electrolyte management therapy is contraindicated.

The SCD-PED cartridge and SCD Blood Tubing Set should not be used on patients who have a known allergy to any of the components in this product.

IV. WARNINGS AND PRECAUTIONS

WARNINGS

1. Carefully read all warnings, precautions, and instructions before use. Follow all operating, maintenance, and installation procedures as described in this document.

2. The blood flow path in the SCD-PED is non-sterile.

3. Operating procedures are only performed by trained and qualified clinicians/personnel.

4. The target post-SCD ionized calcium level during SCD-PED therapy is less than 0.40 mmol/L.

5. The CKRT device and disposables must be operated by trained personnel according to the instructions for use provided by the manufacturer.

6. The use of anything other than the SCD Blood Tubing Set provided by SeaStar Medical may result in patient injury.

7. Do not modify the SCD-PED Cartridge or the SCD Blood Tubing Set in any way.

8. Carefully inspect barriers of all items prior to use. Do not use item if barrier is damaged.

9. The SCD-PED Cartridge and SCD Blood Tubing Set are single use sets . Do not sterilize or reuse the SCD-PED Cartridge. Do not re-sterilize or reuse the SCD Blood Tubing Set.

10. Log or note the lot number of the SCD-PED Cartridge(s) used on a patient in that patient's Electronic Medical Record (EMR) for tracking purposes.

11. During the prime and operation procedures, observe closely for blood/fluid leakage at all circuit connections. If tightening the connections does not stop leakage, immediately replace the SCD-PED Cartridge and the SCD Blood Tubing Set. Leakage can cause blood loss or air entry/air embolism.

12. To prevent contamination, the SCD-PED Cartridge and the SCD Blood Tubing Set must be connected and primed using aseptic technique immediately after opening the packaging and removing caps to make the connections. Use aseptic technique when handling all connections and replacing the SCD-PED Cartridge and the SCD Blood Tubing Set. Universal precautions should be followed to ensure the safety of the patient and clinician.

13. In the event that a patient decompensates (per the treating physician's clinical judgment) within 2 hours of a new SCD-PED Cartridge initiation, SCD-PED therapy should be terminated, and a blood sample should be obtained from the patient and cultured for aerobic, anaerobic, and fungal organisms.

14. Store the SCD-PED Cartridge in a dry place, between 5 °C (41 °F) and 30 °C (86 °F). The upper limit for the SCD Blood Tubing Set is 50 °C (122 °F), with no lower limit specified.

PRECAUTIONS

1. Used SCD-PED Cartridges and SCD Blood Tubing Sets are considered biohazardous materials. Handle and dispose in accordance with hospital policy/procedure and applicable local, state, and federal laws and regulations.

2. Carefully inspect the SCD-PED Cartridge and the SCD Blood Tubing Set prior to use. Do not use the SCD-PED Cartridge and/or the SCD Blood Tubing Set if the package is damaged or if the lines are kinked, or if there is any visual evidence of cracks, breakage, or contamination.

3. The CKRT circuit with SCD-PED Cartridge and SCD Blood Tubing Set connected must be anticoagulated with a continuous citrate infusion during SCD-PED Therapy.

4. Prevent entry of air into the SCD-PED Cartridge or the SCD Blood Tubing Set during set up and priming.

5. Use of SCD-PED with dialysis modalities other than CKRT (i.e., intermittent hemodialysis or peritoneal dialysis) has not been studied.

V. DEVICE DESCRIPTION

The Selective Cytopheretic Device-Pediatrics (SCD-PED) is comprised of tubing, connectors, and a synthetic (b) (4) membrane cartridge.

The SCD-PED Cartridge (with a non-sterile blood flow path) is manufactured by (b) (4) and labeled with a 3-year expiration. SeaStar Medical Inc. provided a letter from (b) (4) authorizing FDA access to a Master File in support of this application.

The SCD Blood Tubing Set is manufactured, packaged, and ethylene oxide sterilized by (b) (4) Tubing Packs are cleared for use in the extracorporeal circuit during cardiopulmonary bypass under (b) (4) is ISO 13485 certified, in addition to FDA 21 CFR Part 820 compliance. The SCD Blood Tubing Set is labeled by (b) (4) as sterile

with a 3-year expiration. Due to the non-sterile blood flow path of the SCD-PED Cartridge, the blood flow path in the SCD-PED device is non-sterile.

The SCD Blood Tubing Set is comprised of the following components:
SCD to Venous Return Line
Hemofilter to SCD Line
Two Luer Adapters for priming
Two zip ties

The SCD-PED cartridge is connected in-line to a commercially available Continuous Kidney Replacement Therapy (CKRT)[1]circuit device as outlined in **Figure 1** below. Blood from the CKRT circuit is diverted after the CKRT hemofilter through to the extra capillary space (ECS) of the SCD. Blood circulates through this space, and it is returned to the patient via the venous return line of the CKRT circuit. The therapeutic post-cartridge ionized calcium level (of < 0.40 mmol/L) for > 90% of treatment time is achieved with Regional Citrate Anticoagulation (RCA) for the entire CKRT and SCD blood circuits.

Figure 1:Schematic of SCD-PED Use

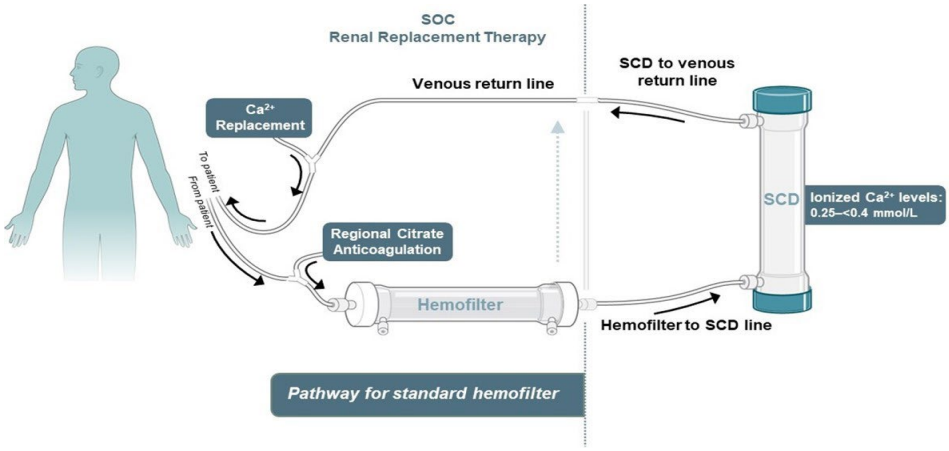

Table 1: SCD-PED Blood Tubing Set Specifications

Priming Volume	35 mL

Table 2: SCD- PED Cartridge Specifications

Applicable Membrane Surface Area	0.98 m^2
Applicable Priming Volume	115 mL
Applicable Max Blood Flow Rate	300 mL/min
Maximum TMP	600 mmHg

[1] Please note that newer term continuous kidney replacement therapy (CKRT) is used interchangeably with the older term continuous renal replacement therapy (CRRT).

VI. ALTERNATIVE PRACTICES OR PROCEDURES

The SCD-PED is intended to be used to treat pediatric patients ≥10 kg with acute kidney injury due to sepsis or a septic condition on antibiotic therapy requiring continuous kidney replacement therapy (CKRT).

Acute kidney injury (AKI) (previously referred to as acute renal failure) describes rapid decline in renal function associated with reduced elimination of waste products, dysregulated electrolyte and acid-base balance, and impaired fluid homeostasis. Acute Tubular Necrosis (ATN) due to ischemia and/or nephrotoxic substances is a leading cause of AKI in both children and adults. The systemic inflammatory response with activation of polymorphonuclear leukocytes (PMNs) and increased production of cytokines and reactive oxygen species (ROS) is thought to contribute to AKI as well as another major organ dysfunction.

AKI occurs in 3.9/1000 at-risk US pediatric hospitalizations; 34.5% of AKI hospitalizations in children required critical care (PICU) during their stay. In critically ill children admitted to PICU, requiring mechanical ventilation and/or vasopressor support, the reported incidence of AKI is over 80 percent. Dialysis is required in 8.8% of AKI cases. The management of AKI begins with prompt evaluation to determine the cause, with special attention to reversible causes. Patients are closely monitored with serial measurements of serum creatinine and urine output to stage the severity of the disease. In early stage 1, the objective of treatment is to optimize the volume status and perfusion pressure to the kidney. Discontinuation of nephrotoxic agents, when feasible, and avoiding iodinated contrast studies are high priorities. As AKI progresses to stage 2, ICU admission for intensive and invasive respiratory / circulatory monitoring and initiation of renal replacement therapy may be necessary. Current standard of care treatment for pediatric AKI includes intermittent dialysis or continuous kidney replacement therapy (CKRT), if hemodynamically unstable. There are no approved therapies in the US to treat the immunomodulatory dysregulation due to pediatric acute kidney injury.

Children with AKI experience poor outcomes with prolonged hospitalization, a greater need for mechanical ventilation, and higher mortality. The multicenter, prospective Assessment of Worldwide AKI, Renal angina, and Epidemiology (AWARE) study, the largest epidemiological study of its kind, demonstrated a stepwise increased correlation between mechanical ventilation use and AKI severity. Patients with stage 1, stage 2, and stage 3 AKI required mechanical ventilation 38.2%, 40.5%, and 50.2% of the time, respectively. The findings from the Kids' Inpatient Database (KID) reveal a longer median length of hospital stay (LOS) for children with AKI. In children with AKI requiring dialysis or AKI-D, the LOS was 21 vs 8 days compared to AKI without need for

dialysis (P< 0.001). For AKI requiring ICU stay, the LOS was 29 vs 6 days to AKI without ICU stay (P< 0.001). Critically ill pediatric patients with AKI severe enough to require dialysis and ICU hospitalization experience mortality rates of 30–50%.

Additionally, children who survive AKI are likely to experience long-term renal dysfunction. Residual renal abnormalities of proteinuria, hypertension, and reduced GFRs persisted in up to 60% of AKI survivors.

VII. MARKETING HISTORY

QUELIMMUNE has not been marketed in the United States or any foreign country.

VIII. ADVERSE REACTIONS OBSERVED DURING THE CLINICAL STUDIES

Five adverse reactions were observed in more than one instance across the two pediatric SCD studies (SCD-PED-01 [16 subjects] and SCD-PED-02 [6 subjects]). The adverse reactions included six instances of hypotension across three subjects, four instances of hypothermia across two subjects, four instances of tachycardia across three subjects, two instances of hyperglycemia across two subjects, and two instances of thrombocytopenia across two subjects.

IX. SUMMARY OF PRECLINICAL STUDIES

LABORATORY

Biocompatibility of the SCD Cartridge is supported by information in the (b) (4) master file. Biocompatibility of the SCD Blood Tubing Set is established under (b) (4) 510(k) (b) (4) for use in an extracorporeal circuit.

(b) (4)

(b) (4)

Shelf life of the SCD Cartridge (with a non-sterile blood flow path) is supported by information in the (b) (4) master file. Sterility and shelf life for the SCD Blood Tubing Set is established under (b) (4) 510(k) (b) (4) for use in an extracorporeal circuit during cardiopulmonary bypass (CPB) surgical procedures.

X. SUMMARY OF CLINICAL INFORMATION

Two clinical trials were conducted in pediatric subjects to evaluate the safety and effectiveness of SCD-PED. These trials are summarized in the table below.

Table 3: Summary of Pediatric Studies

Study/Parameter	SCD-PED-01 (Weight: ≥15 kg)	SCD-PED-02 (Weight: 10-20 kg)	Combined PED-01 and PED-02
No. of subjects (N)	16	6	22
Survival (Day 60)	12 of 16	5 of 6	17 of 22
Survival Rate (Day 60)	75%	83%	77%
Dialysis Independence (Day 60)	12 of 12	5 of 5	17 of 17
Normal Kidney Function (Day 60)	11 of 12	5 of 5	16 of 17

1. PEDIATRIC STUDIES

A. SCD-PED-01

Study SCD-PED-01 was an open-label, single arm, multi-center, externally controlled trial to assess SCD-PED in Pediatric Patients (< 22 years of age)

with AKI, when use in conjunction with CKRT using regional citrate anticoagulation.

Prospect of direct benefit for treating children was derived from an earlier multi-center, randomized, open label, controlled, pivotal study conducted in adults (SCD-003) to evaluate the safety and effectiveness of the SCD when used alone and in conjunction with CKRT. Post Hoc analysis of the per protocol subset in this adult study (n=46) showed 60-day mortality of 16% (3/19) in the SCD group vs 41% (11/27) in the CRRT alone group (p = 0.11).

The primary objective of the SCD-PED-01 study was to evaluate the safety of up to seven consecutive 24-hour SCD treatments. The secondary objective was to evaluate the effectiveness of up to seven consecutive 24-hour SCD treatments on all-cause mortality and dialysis dependency at day 28 and day 60. Exploratory endpoints included time on CKRT, total ICU days, and total hospital days.

Study participants had to be < 22 years of age, weigh > 20 kg, have a clinical diagnosis of AKI due to hemodynamic or toxic etiologies that required CKRT, have no history of CKD, and have at least one non-renal organ failure (defined as receiving mechanical ventilation or at least one vasoactive medication to treat hypotension) or sepsis (proven or suspected). Subjects who had advanced chronic kidney disease, other causes of AKI, severe liver failure, or who were recipients of solid organ or bone marrow transplant were excluded. The subjects were monitored in the intensive care unit (ICU) during the treatment and were followed until death or Day-60, whichever occurred first, with clinical and laboratory assessments at prespecified intervals.

Four pediatric ICUs (Cincinnati Children's Hospital Medical Center, University of Michigan/CS Mott Children's Hospital, University of Alabama at Birmingham/Children's of Alabama, and Emory University/Children's Healthcare of Atlanta at Egleston) enrolled children with AKI and multiorgan dysfunction receiving CRRT to receive the SCD integrated post-CRRT membrane. RCA was used to achieve a circuit iCa^{2+} < 0.40 mmol/L. Subjects received SCD treatment for 7 days or until CKRT discontinuation, whichever came first.

Mean subject age was 12.3 + 5.1 years (range 4 - 21 years), weight was 53.8 + 28.9 kg (range 19.1 - 111 kg), and median PRISM II score at CKRT initiation was 7 (range 2-19). Three subjects weighed less than 24 kg and therefore required blood priming of both the CKRT circuit and SCD hollow fiber cartridge. Three additional subjects weighed from 27.0 to 33.4 kg and required blood priming of the CKRT circuit alone. Two subjects received ECMO. The most common diagnosis leading to ICU admission was septic shock (n = 6), followed by pneumonia (n = 2) and then n = 1 each for rhabdomyolysis, pulmonary hypertension, hemolytic uremic syndrome,

encephalomyelitis, disseminated adenoviral infection, cardiac arrest, acute respiratory failure, and acute liver failure. The indications for initiating CKRT were fluid overload and stage 2 or 3 AKI.

The median duration of SCD treatment course was 6 days (range 1 - 7 days). Four subjects received CKRT for three days or less, and seven subjects received CKRT for between 3 and 5 days. The circuit iCa^{2+} concentrations achieved the threshold of < 0.40 mmol/L for 90.2% of the time subjects received CKRT- SCD therapy. No circuit was lost due to SCD hollow fiber cartridge clotting. The subject systemic iCa^{2+} concentrations were maintained at > 1.0 mmol/L in 97.5% of measurements, with a lowest value of 0.89 mmol/L. Only one subject required a calcium bolus after initiating CKRT-SCD.

The median pre-SCD WBC count was 20.0 x 10^3/mcL (IQR 13.0, 28.1, range 0.37 to 58.1 x 10^3/mcL) and the median platelet count was 113.5 x 10^3/mcL (IQR 94, 266, range 42 to 417 x 10^3/mcL). The lowest WBC and platelet counts were 0.37 x 10^3/mcL and 27 x 10^3/mcL, respectively during the treatment. The potential impact of SCD-PED on leucocytes and platelets is unclear because cell counts could be influenced by multiple factors including antimicrobial therapy and anticoagulation.

Fifteen of the 16 subjects survived to the end of SCD therapy. The one subject who did not survive SCD-PED therapy, died at seven hours of therapy after developing irreversible ventricular tachycardia. Autopsy revealed viral myocarditis. This serious adverse event (SAE) was previously reviewed and the FDA concluded as not related to the device. Three other deaths were observed in subjects at 3, 8, and 16 days after completion of SCD-PED therapy. All three of these subjects required Extra Corporeal Membrane Oxygenation (ECMO). Twelve of the 16 subjects survived to hospital discharge. Of the twelve survivors, ten were dialysis independent at 28 days and all twelve were dialysis independent with normal / baseline serum creatinine at 60 days.

Of the 12 SAEs observed during the study, 6 were adjudicated as unrelated to study (cardiac arrest with viral myocarditis, vascular graft occlusion, adrenal insufficiency, pneumoperitoneum, Steven Johnson's syndrome and nephrolithiasis). The remaining 6 SAEs (2 instances of respiratory failure, 1 instance each of cardiac arrest, cerebral hemorrhage, pulmonary hemorrhage, and junctional tachycardia) were adjudicated as unlikely to be related to the device or the SCD PED procedure.

B. SCD-PED-02

A multi-center, prospective, pilot study was undertaken to assess the safety and effectiveness of the SCD in pediatric subjects between 10-20 kg in weight with AKI being treated with CKRT with regional citrate anticoagulation. The

primary objective of the study was to evaluate the safety of up to ten consecutive 24-hour SCD treatments.

The secondary objective was to evaluate the effectiveness of up to ten consecutive 24-hour SCD treatments on all-cause mortality and dialysis dependency at day 28 and day 60. Exploratory endpoints included total ICU days and total hospital days.

Patients < 18 years old and weighing ≥ 10 kg with a threshold blood pressure of 80/40 mmHg and platelet count ≥15,000/mm^3 at the time of screening who were in the ICU with a clinical diagnosis of AKI requiring CRRT with at least one non-renal organ failure were included in this study. Patients with irreversible brain damage, advanced chronic renal failure at baseline (with eGFR of < 30 ml/min/1.73 m^2), severe chronic liver failure, metastatic malignancy, and chronic immunosuppression were excluded.

The study enrolled six subjects across two investigational sites. Mean subject age was 3.0 years (range 1.6 – 10.4 years), weight was 13.5 kg (range 11.9 – 16.5 kg). Four (4) subjects were male and 2 were female. Median PRISM II score at CKRT initiation was 17.7 (range 12 – 27). All 6 subjects were receiving invasive mechanical ventilation at SCD-PED start. Five (5) patients were septic at SCD-PED start and 5 were on vasopressors. One (1) patient was on ECMO. The median SCD-PED treatment course duration was 4.7 days (range 0.9-8.7 days).

Five (5) subjects survived to Day 28 and Day 60 (5/6; 83%). One subject did not survive due to parental decision to withdraw care on Day 1 post-SCD. The 5 surviving subjects were dialysis independent at day 28 and 60.

Of the 6 SAEs, observed during the study, 3 were unrelated to the device (septic shock, pneumothorax, vascular site thrombosis). The remaining 3 SAEs (cardiac arrest, respiratory failure, lactic acidosis) were unlikely to be related to the device or the SCD -PED procedure.

Discussion of Probable Benefit:

The SCD-PED-01 study was initially conducted as a pilot study in children and subsequently converted to a pivotal study after receiving humanitarian use designation (HUD). A HUD under an HDE is exempt from the requirement of establishing a reasonable assurance of effectiveness that would otherwise be required under sections 514 and 515 of the FD&C Act. Therefore, no formal Statistical Analysis Plan (SAP) was submitted, after the study status was changed to an HDE-eligible study.
The Applicant conducted a comparison of demographics and outcomes between the SCD-PED-01 cohort and a contemporaneous cohort of children receiving CKRT at Cincinnati Children's Hospital (CCHMC). Pediatric Risk of

Mortality Scores Version III (PRISM-III) at ICU admission were used to assess severity of illness. A sensitivity analysis was performed without subjects with primary kidney disease or metabolic disease in the CCHMC group, since such subjects have much lower mortality rates compared to subjects with multiorgan failure who receive CRRT.

The effectiveness analysis revealed ICU survival of 75% for the study cohort and 50% for the matched (based on PRISM II) contemporaneous CKRT population at Cincinnati Children's Hospital (CCHMC). Due to concerns regarding introduction of bias due to unequal distribution of risk factors between the SCD study and the registry, an analysis with subject level matching to ppCRRT database on the most important prognostic indicators (ventilator status (Y/N), vasopressor use (Y/N), age and weight) was conducted. Based on this analysis, the Applicant's own statistical team estimated the overall ppCRRT survival rate to be higher at 62% (95% CI 55-68%) compared to the SCD-PED -01 survival rate of 75% (95%CI 47-92%). In the one-to-many matched analysis, 8-22 subjects in the ppCRRT registry were compared for each subject treated in the clinical study. The FDA statistical team further refined the analysis with equal weighting of each subject and based on that analysis, the ppCRRT survival rate was 65% (95%, CI 58- 71%), compared to the SCD-PED-01 survival rate of 75% (95%CI 47-92%). The FDA concluded that there was an 80% likelihood that the treatment with SCD-PED improved survival or was neutral on survival (compared to population on CKRT without add on SCD-PED).

At the time of ICU discharge, in the SCD-PED-001 study, only 1/12 [8%] of surviving patients in the cohort required dialysis. In the ppCRRT cohort who were ≥15 kg and were either on invasive mechanical ventilation or vasopressor(s) at CKRT initiation, 40/74 (54%) were still on hemodialysis at time of ICU discharge.

At Day 28, only 2 out of 13 subjects required maintenance intermittent hemodialysis.

At Day 60, all 12 survivors were dialysis independent. Because the ppCRRT registry does not include 60-day data, a comparison to ppCRRT patients was not feasible.

With respect to recovery of renal function, all but one of 12 subjects had normal serum creatinine at Day-60 (serum creatinine < 1.0, range 0.39-1.0); the other had serum creatinine of 1.3. The ppCRRT registry does not include information on magnitude and rate of renal recovery upon discharge from the hospital. Hence, FDA relied on data from published literature (case-series reports). The incidence of CKD after recovery of pediatric AKI varied from 34 - 58% based on evidence of CKD, manifesting as hyperfiltration, reduced kidney function, hypertension, or microalbuminuria in a follow-up clinic visits.

Although the duration of follow up in the SCD-PED 01 study was only 60 days and did not use a broader definition of renal dysfunction (including urine abnormalities and secondary hypertension), it is highly encouraging that 92% of subjects had normal renal function by Day 60.

The overall results trended favorably on the clinically meaningful endpoints of survival, dialysis independence, and recovery of renal function, all of which are clinically meaningful for children hospitalized with AKI.

XI. DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

Safety Analysis:

During the SCD-PED-01 study, 4 deaths were reported. FDA concluded that the probability (likelihood) of lower survival rate in the SCD-PED with CKRT population compared to the CKRT population is 12-20%. There were 12 serious adverse events (SAEs) that FDA adjudicated not likely related to the device.

During the SCD-PED-02 study, 1 death (withdrawal of care by parents) was reported. There were 6 serious adverse events (SAEs), which were adjudicated by FDA as unlikely related to the device.

The non-serious adverse events (AEs) observed during these studies include variety of hemodynamic, electrolyte and cell count abnormalities seen in multiple subjects. CKRT is performed in hemodynamically unstable patients. Multitude of electrolyte abnormalities are common and expected in AKI. The cell count abnormalities may have multiple etiologies including underlying cause of AKI in addition to biologic effects of the SCD. It is challenging to reach any conclusions regarding a causal relationship between the device and SAEs, without a concurrent control and a larger database.

Although FDA concludes that the known and probable risks of the device are more than minimal, the reported adverse events or outcomes could likely be

related to underlying disease and the concomitant tests/treatments needed to treat this population and may not be related to use of SCD-PED Device.

FDA's review of safety has the following limitations.

- Study design deficiencies and insufficient sample size make it challenging to detect / attribute SAEs to the device, particularly due to the absence of an internal control.

- The adverse events tracking in the comparator (ppCRRT registry) does not align with MEDDRA (Medical Dictionary for Regulatory Activities) definitions and clinical criteria. Moreover, the registry data is limited to inpatient stay. Therefore, the ppCRRT registry is an imperfect comparator as a control for tracking adverse events either in hospital or out of hospital.

- Even though 3 subjects receiving ECMO died (75% of all deaths) during the study, temporal correlation and severity of underlying illness are confounding factors, making it challenging to assess causality. Because of the critical nature of their underlying illness, these subjects most likely would have required treatment with CKRT (with additional regional citrate anticoagulation). Whether or not, the extent to which the addition of SCD (to the CKRT circuit) may increase the risk of death is not possible to evaluate due to the open-label design given the high baseline mortality risk associated with use of ECMO.

- The fluid-electrolyte abnormalities inherent in AKI, altered calcium levels with citrate anticoagulation, underlying illness including preexisting cardiac conditions, and concomitant interventions make it challenging to attribute any of these SAEs or AEs to the SCD device itself.

Therefore, based on FDA analyses, the following are areas of uncertainty with respect to probable risk:

- Insufficient patient numbers to detect serious events or false positives/false negatives.
- Imperfect comparator method used to calculate performance characteristics.
- Insufficient duration of follow-up to detect delayed or late events.
- Events likely confounded by, and attributed to, other comorbidities or treatment modalities.

<u>Probable Benefit Analysis:</u>

The overall probability that the survival rate of pediatric patients (n=16) with AKI requiring CKRT when they are treated with SCD is neutral or improved compared to CKRT without SCD treatment is 80-88%. The surviving subjects

had a substantial rate of renal recovery (dialysis independence in all 12 survivors). Almost all surviving subjects had near normal renal function at Day-60 (a finding not reported in the published literature).

FDA's analysis of probable benefit has the following limitations:

- The open-label design has the potential for introduction of selection bias with a study population that may have had a lower severity of illness at baseline. However, the reviewers consider that the likelihood of this single arm population having a better prognosis compared to the ppCRRT is low, given that subjects receiving ECMO therapy were enrolled in Study SCD-PED-01 and there were none in the ppCRRT. Therefore, if anything the results were potentially biased against the SCD-PED, because patients on ECMO generally have the poorest prognosis.

- The ppCRRT database is an imperfect comparator because it only follows subjects to end of ICU stay limiting comparisons regarding later mortality, renal function recovery and length of dialysis dependence. The ppCRRT database did not have consistent collection of data on baseline urine output (prior to initiation of CKRT), which is a key prognostic variable. However, access to subject level data for other relevant treatment and prognostic variables. permitted matching with study population.

- The small size of the SCD-PED database and the fact that the results are not statistically significant increase the potential for making false inferences. Statistically significant results to ensure effectiveness are not required for regulatory approval of HDE.

- Lack of standardization of concomitant treatments (e.g., antibiotic use, fluid management, nutritional support, etc.,) reduces the confidence in the results of the study, because it is possible that factors other than the SCD, could have had a greater influence on treatment outcomes than the SCD.

- Because 9/16 subjects in Study SCD-PED came from one study site, the FDA has concerns regarding generalizability of the results because several elements in the protocol were based on institutional guidelines and local practice patterns.

Therefore, the FDA team note the following sources of uncertainty in the benefits that were observed during the study.

- Wide confidence intervals surrounding the point estimate(s) and/or odds ratio(s).

- Large amount of missing data at critical assessment time(s) +/-imputation.

- Impact of confounding interventions or physiological factors.

- Study design or results lead to lack of generalizability for the intended use population or specific clinical subpopulations.

- Imperfect comparator method used to calculate performance characteristics.

Potential risks associated with lack of sterility assurance of the SCD-PED device

Due to the non-sterile blood flow path of the SCD-PED Cartridge, the blood flow path in the SCD-PED device is non-sterile. Risks associated with the use of a non-sterile device include the potential for infection due to microbial contamination of the device. The list of potential pathogens is broad and incubation period is unknown. It is unclear if there are specific microorganisms that can pose a threat to immunocompromised children with AKI.

Additional safeguards outlined below specific to the HDE could mitigate the risks.

- The target population (hemodynamically unstable children with AKI already on CKRT) would be closely monitored in the intensive care unit at appropriately staffed and equipped, highly specialized pediatric hospitals in US.

- Approval by an IRB or an appropriate local committee is required before a HUD under an approved HDE can be used at a health care facility.

- FDA notes that SCD-PED will not be implanted into the body. Therefore, in the event of clinical decompensation of the patient, the extra corporeal circuit containing the device could be easily disconnected and the device can be sent for further analysis.

- FDA recognizes that the facilities may also involve their institutional epidemiology and infection control team(s) to track infection risk associated with use of non-terminally sterile device.

- The Applicant agreed to monitor for new infections in their Post Approval Surveillance Registry with periodic reporting of data to the FDA.

XIII. PANEL RECOMMENDATION:

No Advisory Committee meeting was held on this submission as there were no issues that warranted a panel discussion.

XIV. CBER DECISION

CBER has determined, based on the data submitted in the HDE, that the Selective Cytopheretic Device-Pediatrics (SCD-PED) will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on February 21, 2024.

XV. APPROVAL SPECIFICATIONS

Directions for Use: See device labeling.

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

Post-approval Requirements and Restrictions: See Approval Order.

XVI. REFERENCES

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