STATISTICAL ANALYSIS PLAN (SAP) FOR EUPHRATES TRIAL

Sponsor:	
SPECTRAL INC Diagnostics	Spectral Diagnostics (US) Inc 20201 Century Boulevard Germantown, Maryland 20874
Protocol Number:	SDI-PMX-NA001
Protocol Title:	**E**valuating the **U**se of **P**olymyxin B **H**emoperfusion in a **R**andomized controlled trial of **A**dults **T**reated for **E**ndotoxemia and **S**eptic shock (EUPHRATES)
Protocol Date / Version:	11Aug2015/ Version 9.1

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Plan Version:	Version 7.0
Plan Date:	4April2016

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Protocol Title:	**Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock (EUPHRATES)**
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Version:	SAP Version 7.0
Date:	4April2016

I have read and approve the Statistical Analysis Plan specified above and agree on its content:

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ABBREVIATIONS, ACRONYMS, AND DEFINITIONS

Abbreviation/Acronym	**Definition**
AE	Adverse Event
ADE	Adverse Device Effect
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ANCOVA	Analysis of Covariance
APACHE II Score	Acute Physiology, Age and Chronic Health Evaluation II
ASA	American Statistical Association
ATC	Anatomic Therapeutic Classification
C4	Cooper Clinical Coordinating Center
CI	Confidence Interval
CP	Conditional Power
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTC	Common Terminology Criteria for AEs
CVI	Cumulative Vasopressor Index
DSMB	Data Safety Monitoring Board
EAA	Endotoxin Activity Assay
ECG	Electrocardiogram
EUPHAS2	Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock 2 – The Registry
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MAP	Mean Arterial Pressure
MMRM	Mixed-Effect Model Repeated Measure model
MODS	Multiple Organ Dysfunction Score
MV	Mechanical Ventilation
PMX	Polymyxin b cartridge (TORAYMYXIN PMX-20R column)
PP	Per Protocol
PT	Preferred Term
RRT	Renal Replacement Therapy

SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SCr	Serum creatinine
SDI	Spectral Diagnostics Inc.
SOC	Standard of Care
VP	Vasopressors
USADE	Unanticipated Serious Adverse Device Effect
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses and reporting for the clinical trial protocol SDI-PMX-NA001, sponsored by Spectral Diagnostics, (US) Inc. The study is being conducted under the US Food and Drug Administration (FDA) Investigational Device Exemption (IDE) Number G090151.

The main objective of this study is to compare the safety and efficacy of the PMX cartridge versus standard of care alone in the treatment of adult patients who have septic shock that is accompanied with a high blood level of endotoxin (i.e., endotoxemia). Subjects in Intensive Care Units (ICUs) will be assessed for septic shock using suspicion of infection and hypotension requiring vasopressor support as primary criteria. After a subject (or suitable surrogate) provides consent, the presence of an elevated endotoxin level ($\geq$ 0.60 EAA units) will be determined, using the Endotoxin Activity Assay (EAA). Consented subjects meeting the required EAA level and the other protocol entrance criteria will be randomized to either the PMX cartridge or a sham treatment. Randomized subjects will receive two PMX cartridge hemoperfusions (or two sham treatments) approximately 24 hours apart. The primary endpoint (mortality) will be assessed 28 days after treatment and subjects in both treatment groups will be followed for mortality assessment for a duration of 12 months.

The reader is encouraged to review the complete protocol, as this plan contains only a limited overview of protocol information. The main objective of this SAP is to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

The format and content of this plan are structured to provide sufficient detail to meet the requirements specified by the International Conference on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. All work planned and presented in this plan will follow the ethical guidelines published by the American Statistical Association (ASA).

The following documents and references 1 through 5 in Section 10 were reviewed in preparation of this plan:

- All protocol versions/amendments through Protocol Version 9.1
- All FDA correspondence to date
- Randomization Plan Version 1 (Jan25, 2012) and Version 2 (Jun 18, 2015)
- Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics (February 2010)
- US Federal Register, Department of Health and Human Services, FDA, Guidance on Statistical Principles for Clinical Trials (1998)
- ASA Ethical Guidelines for Statistical Practice (1999)
- The Royal Statistical Society: Code of Conduct (1993)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998)

2. PROTOCOL DESIGN

2.1 Design Overview

This clinical trial is a double-blind, randomized, parallel group, controlled, multi-center study. It is designed to compare the safety and efficacy of hemoperfusion with the PMX cartridge plus standard of care vs. a sham hemoperfusion plus standard of care based on mortality at 28-days in subjects with septic shock who have high levels of endotoxin.

The PMX cartridge is a single-use extracorporeal hemoperfusion device used to remove endotoxin from patients' blood through direct adsorption onto immobilized Polymyxin B that is contained in the cartridge. For this protocol, subjects will receive either the PMX cartridge or sham perfusion twice in a 24-hour time period.

Subjects in ICUs will be assessed for septic shock using suspicion of infection requiring antibiotic administration and hypotension requiring vasopressor support as the primary criteria for eligibility. As a final eligibility criterion, subjects (or a surrogate decision maker) will consent to a blood draw to determine the presence of an elevated endotoxin level ($\geq$ 0.60 EAA units) using the EAA.

If the EAA is elevated ($\geq$ 0.60 EAA units) and the full inclusion/exclusion criteria are met, as confirmed by the Cooper Clinical Coordinating Center (C4), the consented

subjects will be randomized to receive either standard medical care for septic shock plus a sham hemoperfusion (performed twice, approximately 24 hours apart), or standard medical care plus the PMX cartridge hemoperfusion (administered twice, approximately 24 hours apart). The status of all subjects will be followed by clinicians, which will include measurement of endotoxin levels using EAA. Subjects will be followed, daily, to Day 3 (approximately 72 hours after randomization), again at Day 7, and weekly through Day 28 (-6, +1 days). For all randomized and treated subjects, a follow-up visit or telephone call will take place approximately 90 days (± 1 day), 6 months (±7 days), and 12 months (±7 days) post start of treatment. The schedule of assessments for this study is presented in Table 2-1.

Analysis of the primary efficacy outcome will occur at the completion of the 28-day assessment. Every effort will be made to obtain the mortality status for ALL randomized subjects at the 28-day, the 90-day, the 6-month, and 12-month timepoints, regardless of treatment disposition or withdrawal status.

Approximately 60 clinical sites in the U.S. and Canada will participate in this study, with an expected enrollment of 446 subjects (223 per treatment arm). However, the primary population for analysis will be 176 (88 per arm) plus up to 15% for attrition for a maximum expected enrollment of 478.

Table 2-1 Schedule of Assessments

Assessment	Screen[1]		Baseline[2]	Treatment			Post Treatment				Long Term Follow -Up		
	Primary	Secondary	Day 0	Day 1[10]	Day 2[11]	Day 3[12]	Day 7(±1)	Day 14(±1)	Day 21(±1)	Day 28[6]	Month 3 (±1 Day)	Month 6 (± 7 Days)	Month 12 (± 7 days)
Admission to ICU (date/time)	X												
Informed Consent for EAA	X												
EAA		X		X[3]	X	X[4]	X	X	X	X			
Informed Consent for Randomization		X											
Inclusion/Exclusion Criteria	X	X	X										
Pregnancy Test[8]			X[2]										
Demographics			X										
Medical/Surgical History			X										
Physical Exam			X[2]							X			
Vital Signs[14]			X	X	X	X	X	X	X	X			
12 Lead ECG			X[2]							X			
Microbiology Culture[5]			X	Record any other results collected as part of Standard of Care									
Laboratory Assessments[7]	X		X[2]	X	X	X	X[15]	X[15]	X[15]	X			
Urinalysis			X[2]							X			
Renal function (urine output)			X[2]	X	X	X							
APACHE II Scoring			X[2]										
Organ Function	X			X	X	X							

(continued on next page)

Table 2-1 Schedule of Assessments (continued)

Assessment	Screen[1]		Baseline[2]	Treatment			Post Treatment				Long Term Follow -Up		
	Primary	Secondary	Day 0	Day 1[10]	Day 2[11]	Day 3[12]	Day 7(±1)	Day 14(±1)	Day 21(±1)	Day 28[6]	Month 3 (±1 Day)	Month 6 (± 7 Days)	Month 12 (± 7 days)
(MODS) Scoring													
Mechanical Ventilation Use	X		X[2]	X	X	X	X	X	X	X			
Assess RRT Use			X[2]	X	X	X	X	X	X	X			
Vasopressor Use	X	X	X[2]	X	X	X	X	X	X	X			
CVI score			X	X	X	X							
Randomization[9]			X										
PMX Cartridge or Sham				XX									
Mortality Status[13]										X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X			
Adverse Events[2]			X	X	X	X	X	X	X	X	X	X	X

1. The screening period is defined as the interval of time from 2 hours after onset of vasopressor therapy to the time of randomization
2. Baseline is defined as starting at the time of randomization to the initiation of the study perfusion. Assessments for baseline recording can be performed during the primary and secondary screening period, i.e. -12h to initiation of treatment at the exception of the following:
   -Blood cultures may be drawn up to 24 hr prior to randomization, or anytime during baseline
   -Urine output may be collected over a maximum of 24 hr prior to the first treatment
   -Vital signs may be measured within 4hr of randomization.
   - All adverse and safety events begin at dialysis line or SHAM line insertion.
3. EAA performed 10 hours (+/- 30 minutes) after the completion of each PMX cartridge administration or sham perfusion
4. Blood sample for EAA to be obtained on scheduled days as long as subject remains in hospital. Results after the screening sample are to remain blinded
5. Two sets of blood cultures (aerobic and anaerobic for each set) must be drawn for baseline assessment and results recorded in the CRF for baseline (day 0) assessments. Results are not required prior to randomization. Any other microbiology cultures collected as part of Standard of Care from Day 1 to Day 28 will be recorded on the Microbiology Culture results page in the CRF, including those with a report of "no growth".

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Table 2-1 Schedule of Assessments (continued)

6. There is a window of (-6/+1 days) for Assessments for patients alive on Day 28. However, the mortality determination should be done at least 28 days post first treatment or later.
7. Lab assessments include hematology, chemistry and coagulation
8. To be performed on females of childbearing potential
9. Eligibility confirmation conducted through the Cooper Clinical Coordinating Center (C4); randomization is generated through a central source and is conducted through local pharmacies
10. Day 1 will be designated as the 24 hour period from the start of the first treatment to the end of the second treatment (PMX cartridge/sham perfusion)
11. Day 2 is designated as the 24 hours after the second PMX cartridge/sham perfusion has been completed. The Day 2 assessments will take place approximately 10 hours (± 2 hours) after the completion of the 2nd PMX cartridge/sham perfusion
12. Day 3 will correspond to the 24 hour interval after Day 2. The Day 3 assessments will be made no earlier than 24 hours after the Day 2 assessments were performed, and no later than the end of Day 3.
13. Mortality status confirmation on day 28 (or later),day 90 (±1 day) and at 6 month (+/- 7 days and 12 months (+/- 7days) via telephone contact or visit, if subject remains in study hospital
14. O_2 saturation may be obtained from electronic monitor
15. These lab tests are required only if they are the study site/s standard of care and collected within the protocol-specified window (i.e., these labs are not required if they are not the site's standard of care; additionally, these labs are not required if they are standard of care for the site but collected outside the protocol-specified window)

Source: Protocol, Version 9.1

2.2 Clinical Trial Duration

The duration of treatment plus the active follow-up for each subject will be from the randomization date until 28 days post-randomization date. There will be three additional follow-up visits, at 90 days, 6 months, and 12 months post randomization. The mortality status of subjects who survive beyond the 28-day post randomization time period will be assessed at the follow-up visits.

All subjects who are discharged from the hospital prior to Day 28 will be requested to have End of Study/Early Termination assessments (originally scheduled for Day 28) at the time of hospital discharge, followed by a telephone contact at Day 28, Day 90, Month 6, and Month 12 to assess mortality.

2.3 Clinical Trial Treatments

2.3.1 Treatment Groups

There are two treatment groups in this trial. The two treatment groups to be evaluated are described in Table 2-2, below.

Table 2-2 Treatment Groups

Study Treatment	Treatment Description
Standard of Care + PMX Cartridge Hemoperfusion	Standard medical care for septic shock following the principles of the current Surviving Sepsis Campaign (SSC) International Guidelines for Management of Severe Sepsis and Septic Shock + Hemoperfusion with the PMX cartridge (a single use extracorporeal hemoperfusion device used to remove endotoxin from patients' blood through direct hemoperfusion)
Standard of Care + Sham Hemoperfusion	Standard medical care for septic shock following the principles of the current Surviving Sepsis Campaign (SSC) International Guidelines for Management of Severe Sepsis and Septic Shock + Sham hemoperfusion

2.3.2 Randomization and Method of Treatment Assignment

All subjects will be randomized to one of the two treatment groups presented in Table 2-2. The randomization to treatment will be in a 1:1 ratio (i.e., PMX Cartridge: Sham Hemoperfusion) and stratified by study site.

A "Randomization List" (containing the sequence of treatment group assignment for subjects at each site) will be generated by the independent statistician and either delivered to the study pharmacist in a sealed envelope or maintained by a secured internet-based randomization system. This form and the internet-based randomization system will have the randomization sequence for the site and will have the information to dispense treatment (PMX cartridge or sham) to each eligible subject.

After subject eligibility is established by qualified study personnel at the clinical study site, the Cooper Clinical Coordinating Center (C4) will confirm subject eligibility via a telephone interview with the enrolling site. After receipt of C4's confirmation of eligibility, the study designate will randomize the subject to one of the two study treatments using the "Randomization List" described above. Only the study designate at the study site will have access to the randomization schedule. For more detail, please review the randomization plan.

2.3.3 Blinding

The study subjects, ICU physician investigators, and all ICU health care professionals (except for the bedside ICU nurse), and those who are involved in data analysis (except an independent statistician), will remain blinded to allocation of treatment through the day 28 mortality assessment. However, the nephrologists involved in the hemoperfusion (or their technician designates), the ICU bedside nurse and assigned pharmacist will know the treatment allocation and will be trained to record data onto case report form (CRF) pages that are kept blinded from the rest of the study personnel. They will document the treatment allocation by recording only the device serial number (as indicated on the device/sham carton), the timing of device/sham use, adverse events (noted during the course of treatment) and concomitant anticoagulation administered (e.g. heparin) as necessary.

In order to maintain the blind for subjects, the nephrology staff will be trained on both

the use of the PMX cartridge and the sham perfusion.

The final treatment unblinding (i.e., data lock) and analysis for the study will occur after all subjects have completed the study through the 28-day follow up visit and after all of these clinical data have been received, and data inconsistencies have been resolved. However, the individual subject treatment may be unblinded for safety reasons on a case by case basis (i.e., emergency unblinding). The processes for unblinding and emergency unblinding are outlined in the Randomization Plan. Please refer to the Randomization Plan for more details.

In addition, any subject that was unblinded for any reason prior to the subject's day 28 mortality assessment will be identified and discussed in the final clinical study report.

2.4 Protocol Objectives

The primary objective of this trial is to compare the safety and efficacy of hemoperfusion with the PMX cartridge vs. a sham hemoperfusion based on mortality at 28 days in subjects with septic shock who have high levels of endotoxin. Subjects in both treatment groups will be treated with standard medical care.

The secondary objectives (which include both secondary and exploratory efficacy endpoints) are outlined below. Note: these are not ordered in terms of importance or statistical evaluation.

- To compare mortality between the two groups at 14 days, 90 days, 6 months and 12 months post start of treatment
- To compare the change in endotoxin levels between the PMX cartridge treated group and the control group at approximately 12 hours after completion of a second PMX cartridge and from baseline through day 7, with a treatment target of a > 15% reduction of EAA levels with PMX cartridge treatment
- To compare the changes in vasopressor doses using the cumulative vasopressor index (CVI) for the two groups from Day 0 to Day 3
- To compare the number of days of need for vasopressors in each group from Day 0 to Day 28 (days alive and off vasopressors)
- To compare changes in mean arterial blood pressure (MAP) for the two groups from Day 0 to Day 3
- Comparison of the changes in renal function from day 0 to Day 3:
- Urine output
- Serum creatinine

- To compare the effects of two uses of the PMX cartridge on progression of, and recovery from, organ dysfunction using the Multiple Organ Dysfunction Score (MODS) from Day 0 to Day 3
- To compare the number of days of need for renal replacement therapy (RRT) in each group from Day 0 to Day 28 (days alive and off RRT)
- To compare the number of days of need for mechanical ventilation (MV) in each group from Day 0 to Day 28 (days alive and off MV)
- To compare the mean number of days spent in the hospital by subjects in each group for survivors to Day 28
- To compare the survival time from baseline to death within 28 days
- To compare the survival time from baseline to death within 90 days, 6 months and 12 months.
- Change in kidney function from baseline to 72 hours (Day 3), as assessed by the composite Acute Kidney Injury (AKI) score

2.5 Efficacy Assessments

The following efficacy outcomes will be evaluated to compare the subjects who were treated with standard of care alone (i.e., standard of care plus sham hemoperfusion) compared to those that received the standard of care plus hemoperfusion with PMX cartridge.

2.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is to assess the efficacy of the PMX cartridge based on the mortality rate at 28 days (i.e., the difference in percent of deaths between the two treatment groups).

2.5.2 Secondary Efficacy Endpoints

The secondary endpoints presented below will also be evaluated so to assess the secondary objectives of the trial. These endpoints are sequenced according to the order that they will be tested under the Closed Test Procedure (described in Section 9.2.2 of this document).

1. Survival time from baseline to death within 28 days
2. Change in organ dysfunction from completion of therapy to 72 hours (Day 3), as assessed by the total Multiple Organ Dysfunction Score (MODS)
3. Change from baseline to Day 3 in mean arterial pressure (MAP)
4. Change in renal function from completion of therapy to 72 hours (Day 3), as assessed by urinary output

5. Change in renal function from completion of therapy to 72 hours (Day 3), as assessed by serum creatinine values

2.5.3 Exploratory Efficacy Endpoints

The exploratory efficacy outcomes for this study, which satisfy the remaining secondary protocol objectives, include the following:

- Change in respiratory function from baseline to 72 hours (Day 3), as assessed by the pO_2/FiO_2 ratio used in determining the MODS
- Change in hepatic function from baseline to 72 hours (Day 3), as assessed by total bilirubin values used in determining the MODS
- Change in hematologic function from baseline to 72 hours (Day 3), as assessed by platelet counts used in determining the MODS
- Change in kidney function from baseline to 72 hours (Day 3), as assessed by the composite Acute Kidney Injury (AKI) score
- Changes in the Cumulative Vasopressor Index (CVI) from baseline to 72 hours (Day 3)
- Comparison of the number of days alive and free of Renal Replacement Therapy (RRT) from Day 0 through Day 28
- Comparison of the number of days alive and free of vasopressor use from Day 0 through Day 28
- Comparison of the number of days alive and free of mechanical ventilation from Day 0 through Day 28
- Comparison of the mean number of days spent in the hospital by subjects in each group for survivors to Day 28
- Comparison of the mean number of days spent in the hospital by subjects in each group for survivors to Day 90, Month 6, and Month 12
- Change in endotoxin levels, as assessed by EAA, from baseline to 12 hours after completion of treatment (defined as 2 administrations of PMX cartridge or sham treatment)
- Change in endotoxin levels, as assessed by EAA, from baseline through Day 7

- Mortality rate at 28 days for the following subgroups, PMX treatment vs. sham treatment
    - subjects with a documented infection (any type)
    - subjects with a documented Gram negative infection
    - subjects with a documented Gram positive infection
    - subjects with a documented mixed infection
    - subjects with no documented infection
    - subjects with a pulmonary (lung) infection (either suspected or documented)
    - subjects with an infection other than pulmonary (either suspected or documented)
    - subjects with baseline AKI score of 1 – 4, inclusive
- Survival time from baseline to death within 90 days
- Survival time from baseline to death within 6 months
- Survival time from baseline to death within 12 months
- Mortality at 90 days, 6 months, and 12 months

2.6 Safety Assessments

The safety outcomes will assess the overall safety of the patients via the incidence of adverse events and adverse device effects, as well as changes in chemistry, hematology, and urinalysis laboratory parameters, physical examinations, electrocardiograms, and vital signs.

Specifically, safety assessments for this clinical trial include the following assessments:

- Changes in vital signs
- Changes in blood chemistry and hematology
- Changes in coagulation parameters
- Changes in urinalysis
- Changes in ECGs
- Incidence, investigational product relationship, and severity of adverse events (AEs) and adverse device events (ADEs)

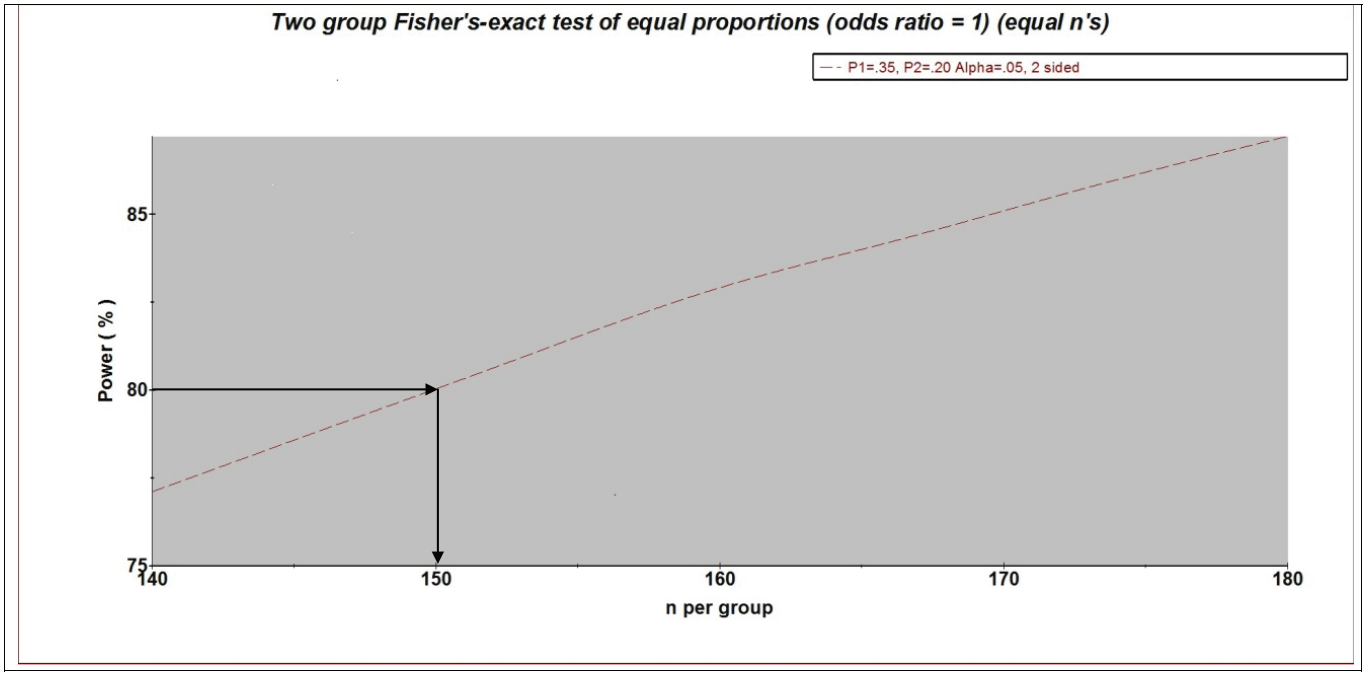
3. SAMPLE SIZE

3.1 Original Sample Size Determination, Statistical Power, And Significance Level

The study will randomize up to 360 subjects (i.e., 180 subjects per treatment arm). This number includes an attrition rate.

The sample size calculation is based on the assumption that there is a clinically meaningful difference of 15% between the proportions of death, within 28 days, for the two treatment groups (i.e., 35% deaths in subjects treated with standard of care plus sham hemoperfusion vs. 20% deaths in subjects treated with standard of care plus the PMX cartridge hemoperfusion). Additionally, this sample size estimate is based on a two-sided test with a type I error rate of 0.05, at least 80% statistical power, and an estimated 15% attrition rate from the randomized subjects of each study arm. The required sample size without any attrition is 306 (153 per treatment arm), as depicted in Figure 3-1. All statistical tests will be two-sided and a 5% significance level maintained throughout the analyses.

Figure 3-1: Sample Size, Based on Fisher's-Exact Test



3.2 Sample Size Recommendation Post Efficacy Interim Analysis

Per the recommendation from the DSMB the sample size of the study is increased and it is planned to randomize up to 650 subjects (i.e., 325 subjects per treatment arm).

3.3 Sample Size Recommendation per FDA comments

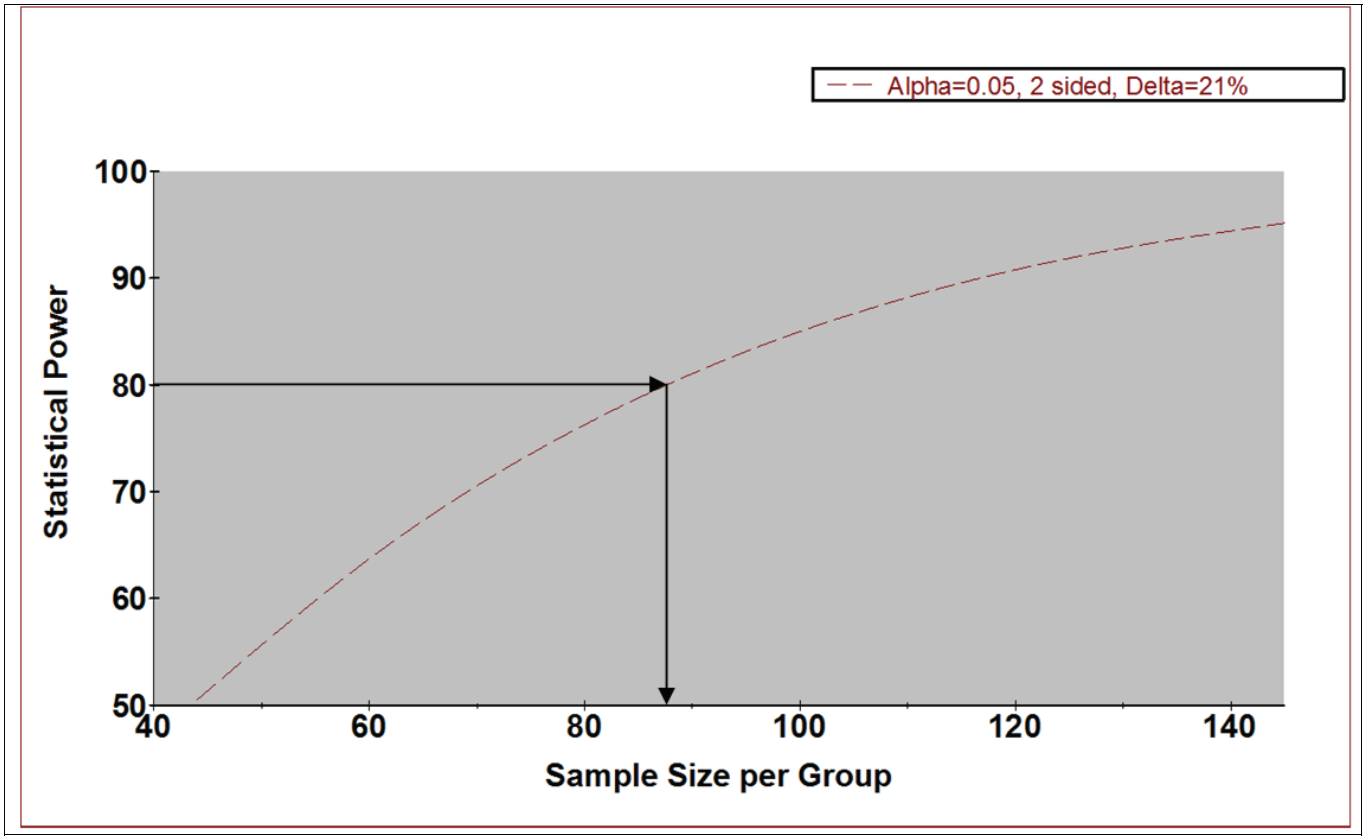
Per the recommendation from the FDA the population for the primary analysis of this trial is patients randomized after 9April2014 rather than all patients randomized since the start of the trial.

Since the addition of the exclusion criteria (MODS ≤ 9), the composite mortality in the post 9April2014 population is substantially higher (ranging from 48-52%) than the estimated mortality prior to this exclusion criteria.

The sponsor in conjunction with the steering committee would like to perform a sample size adjustment based on the observed high event rate in addition to the FDA's preference for the primary population being post 9April2014. Patients who matched the eligibility criteria for EUPHRATES were selected from the EUPHAS 2 registry (Registry for PMX use in patients with endotoxemia and septic shock). The mortality rate of these subjects who received Standard of Care plus PMX cartridge in EUPHAS 2 is 37.5%. The composite mortality rate for subjects in EUPHRATES [SDI-PMX-NA001] post 9April2014 as of 14July2015 is 48%. Therefore the approximated delta is 21%.

The following sample size estimate is based on a two-sided test with a type I error rate of 0.05, at least 80% statistical power, and an estimated 2% attrition rate from the randomized subjects of each study arm. The required sample size without any attrition is 176 (88 per treatment arm), as depicted in Figure 3-2. The required sample size with 2% attrition is 180 (90 per treatment arm). All statistical tests will be two-sided and a 5% significance level maintained throughout the analyses.

Figure 3-2: Sample Size



4. HYPOTHESIS TO BE TESTED

This clinical trial is designed to primarily test the hypothesis that hemoperfusion with the PMX cartridge in this patient population (i.e., subjects in septic shock with endotoxemia) provides a lower mortality percentage at the end of the first 28 days (from clinical and statistical viewpoints) than for those treated with the best currently available treatment (Standard of Care). Hence, the statistical inference will be done on P_{PMX} (i.e., the proportion of death within 28 days for the arm of standard medical care plus PMX cartridge) vs. P_{soc} (i.e., the proportion of death within 28 days for the arm of standard medical care alone); that is the following hypothesis will be examined:

H_0: $P_{PMX} = P_{soc}$ (i.e. the proportion of death within 28 days between the two groups is the same)

H_1: $P_{PMX} \neq P_{soc}$ (i.e. there is difference in the proportion of death within 28 days between the two groups)

5. INTERIM ANALYSIS

Two separate interim analyses are planned for this trial. The first interim analysis will be conducted for safety and the second will be primarily for efficacy. The second interim analysis will have prospectively assigned stopping rules and a method to protect the type I error rate and the integrity of the trial, as hypothesis testing at the second interim analysis is planned.

Both interim analyses will be conducted under the auspices of an independent Data Safety Monitoring Board (DSMB). The timing, purpose, and procedures for these two interim analyses are detailed and discussed in Section 5.1 and Section 5.2, below.

To protect the integrity of the blinded data, both interim analyses will be conducted based on Amarex's Standard Operating Procedure for Interim Analysis and DSMB Preparation (Amarex, SOP BM007, see reference 9 in Section 10). This SOP has a well-established firewall to protect the integrity of blinded trials. And, the only information that will be released to the sponsor will be the information that is described in this SAP; i.e., Section 5.1 and Section 5.2.

To protect the trial-wise type I error rate, the adjustment to the type I error rate for the final analysis is be predefined and detailed in this SAP. The need for the adjustment of type I error rate of alpha is due to the unblinded look and the planned statistical inference that will be conducted at the time of the second interim analysis. This adjustment is detailed in Section 5.2.

5.1 Safety Assessment Analysis (1st Interim Analysis)

Timing:

This safety assessment analysis will be conducted after approximately 20% of the required population (76/360 treated subjects) have completed the 28-day post-treatment observation period or have died (or were withdrawn) before completing the 28-day post-treatment observation period.

Goals:

The objective of this safety assessment analysis to ensure subject safety by DSMB review of the unblinded data

Analysis Population:

All subjects who have been randomized and treated when the 76th subject completes the 28-day post treatment period or have died (or were withdrawn) before completing the 28-day post treatment period will be included in the analysis. All available data from these subjects will be included in the analysis.

Procedures:

a. Cut-off dates for collection of CRFs, data cleaning, database lock and analysis will be established based on an estimated target date of the 76th treated subject completing the 28-day post-treatment observation period.
b. All data received by the cutoff date will be entered, validated, queries generated and resolved or pending queries documented.
c. The database will be locked for the interim analysis. This database will not contain the treatment assignments (i.e., will be blinded).
d. The locked database will be saved in a drive to which only the independent statistician responsible for the interim analysis has access.
e. The randomization code to un-blind the data will be delivered to the independent statistician by the randomization code generator.
f. The independent statistician will merge the randomization code with the validated

data and will generate planned data and information for the DSMB, as described below.

Data and Information Provided to DSMB:

The DSMB will receive the following data: AEs, SAEs, labs, ECGs, vital signs, and all other safety related variables identified per the DSMB Charter. No inferential statistics will be conducted for this interim analysis.

All data and summaries provided to the DSMB will be identified by masked treatment groups (e.g., Group A and Group B). Codes to the actual treatments will be provided upon request of the DSMB chairperson.

Stopping Rule:

There is no intention of stopping the study as a result of this interim analysis. However, DSMB may recommend stopping the trial for safety reasons at any time.

Information Provided to Sponsor by DSMB:

Following each meeting, formal minutes, including any recommendations for continuation or modification of the trial, will be prepared according to the procedure outlined in the DSMB Charter. These minutes will not contain any information or comments that might possibly unblind the trial.

Type I Error Rate Adjustment:

No type I error adjustment will be made due to this safety analysis.

As there are no planned inferential statistics, the type I error rate for the final analysis will not be inflated because of this interim analysis.

5.2 Efficacy Assessment Analysis (2nd Interim Analysis)

Timing:

This efficacy assessment analysis will be conducted when approximately 50% of the planned population (184/360 treated subjects) have completed the 28-day post-treatment observation period or have died (or were withdrawn) before completing the 28-day post-treatment observation period.

Goals:

The objectives of this interim analysis are:

- to evaluate the safety and efficacy of PMX Cartridge.
- to determine if there is sufficient statistical rational (i.e., a small enough type I error rate), clinical, or ethical justification to stop the trial.
- if the trial is not terminated based on the interim analysis, the results of the interim efficacy analysis will be used to revise sample size estimations, which will serve in the planning of the remaining trial. An independent statistician will conduct the power analyses.

Analysis Population:

All subjects who have been randomized and treated at the time that the 184th subject completes the 28-day post treatment period or have died (or were withdrawn) before completing the 28-day post treatment period will be included in the analysis. All available data from these subjects will be included.

Procedures:

a. Cutoff dates for collection of CRFs, data cleaning, database lock and analysis will be established based on an estimated target date of the 184th treated subject completing the 28-day post-treatment observation period.
b. All data received by the cutoff date will be entered, validated, queries generated and resolved or pending queries documented.
c. The database will be locked for the interim analysis. This database will not contain the treatment assignments (i.e., will be blinded).
d. The locked database will be saved in a drive to which only the independent statistician responsible for the interim analysis has access.
e. The randomization code to un-blind the data will be delivered to the independent statistician by the randomization code generator.
f. The independent statistician will merge the randomization code with the validated data and will generate the planned inferential statistical analyses for the primary efficacy endpoint and a statistical report for the DSMB, as outlined below.

Data Provided to DSMB:

In addition to the data that is required for standard DSMB quarterly meetings, the DSMB will receive a statistical report that includes the following:

- Summary table of mortality rate within 28 days after randomization, containing

descriptive and inferential statistics, as outlined in Section 9.2.1.

- Description/statistical interpretation of the type I error and the effect of the efficacy analysis.
- The description/statistical interpretation conditional power (CP) at the time of this interim analysis.
- CP will be calculated according Chen 2004 (see reference 8 in Section 10) using primary endpoint data. This CP will be used to determine whether the sample size needs to be increased.

All data and summaries provided to the DSMB will be identified by masked treatment groups (e.g., Group A and Group B). Codes to the actual treatments will be provided upon request of the DSMB chairperson.

These data will be provided ONLY to DSMB members.

Stopping Rule:

Termination of the study due to efficacy results at this interim analysis will require a p-value of less than 0.005; according to the O'Brien-Fleming approach (see reference 6, Section 10).

Information Provided to Sponsor by DSMB:

The DSMB will make recommendations to sponsor on the continuation / modification / termination and relevant comments based on the un-blinded results.

Type I Error Rate Adjustment:

O-Brien Fleming Approach (see reference 7, Section 10) will be used to address the type I error rate adjustment to protect the trial-wise Type I error at the final analysis.

6. ANALYSIS POPULATIONS

6.1 Intent-to-Treat Population

The Intent-to-treat (ITT) population is defined as all subjects that have been randomized to receive either PMX treatment or the sham treatment.

The primary analyses population will be subjects who were randomized after 9April2014. NOTE: all cases where a subject is randomized but does not receive treatment will be identified and summarized by randomized treatment group; and the reason for not receiving the study intervention will be described.

6.2 Per Protocol Population

The Per Protocol (PP) patient population is defined as the subjects that have received both treatments with the PMX cartridge or sham treatments and did not have any major protocol violations.

The PP population will be used as a supportive analysis if there is at least 5% difference between the numbers of subjects in the two populations.

6.3 Safety Population

The safety population is defined as all subjects who have signed informed consent for treatment randomization and for whom the treatment has, at least, been initiated.

Treatment initiation is defined as the start time for actual or sham placement of the central line for treatment.

This population will be used for the analysis of all safety parameters.

7. DATA CONVENTION AND RELATED DEFINITIONS

7.1 Baseline Definition

For all parameters, baseline will be defined as the last available value before initiation of the first randomized treatment.

7.2 Duplicate Data

For unplanned duplicate data within a protocol-specified scheduled visit, the last measured value will be used for the analysis. If it is not possible to identify the "last measured value" the average of the duplicate values will be used.

No data will be excluded. All collected data will be listed.

7.3 Handling of Missing Data

For efficacy evaluation data points, the following methods will be used for post baseline time points with missing assessments:

- If the missing data point is continuous in nature:
    - Mixed-Effect Model Repeated Measure (MMRM) model will be used to

adjust for the missing values for the endpoints that would be analyzed using general linear mixed effect models

- Last Observation Carried Forward (LOCF) will be used for those endpoints that would be analyzed using a different methodology than general linear mixed models

- For mortality analysis subjects with unknown survival status will be excluded from the primary analysis. In addition, sensitivity analyses will also be performed to account for subjects with unknown survival status (i.e., two analyses will be performed: (1) all subjects with unknown survival status will be assumed to be dead at Study Day 28 and (2) all subjects with unknown survival status will be assumed to be alive at Study Day 28.
- For time-to-event analysis of mortality, subjects with unknown survival status will be censored at the last date for which the subject was known to be alive or in the study hospital.

7.4 Multicenter Clinical Trials

This is a multi-center study using a by-site randomization with a small expected patient enrollment per site. For this reason, there are no plans to use investigative site as a covariate in the analyses models.

7.5 Multiple Comparisons and Multiplicity

For the primary endpoint only one hypothesis will be tested; however, there is a planned unblinded look at the primary endpoint data with statistical inference planned to be performed at the time of the second interim analysis. For this reason, O-Brien Fleming Approach (see reference 7, Section 10) will be used to address the type I error rate adjustment in order to protect the trial-wise type I error at the final analysis. Using this approach, a portion of the trial-wise type I error rate (0.05) will be spent (or allocated) to the second interim analysis. The adjusted type I error rate for the final analysis will be 0.048 in order to conclude that the study regimen is effective.

For the secondary endpoints, the closed test procedure (see reference 10, Section 10) will be used to protect the type I error rate. Please see Section 9.2.2 for the order of the

secondary endpoints. Any of the secondary endpoints can generate additional claims or included in the clinical trial section of the product label if they are declared to show a statistically significant difference provided the final adjusted type I error rate of 0.048 is used.

7.6 Conditional Power for Sample Size Re-estimation

The conditional power at the time of the second interim analysis will be calculated for the primary endpoint using the following formula:

$$CP(f_1,z_1) = \Phi \left\{ z_1 / \sqrt{f_1 (1 - f_1)} - z_\alpha / \sqrt{(1 - f_1)} \right\}$$

Where:

- $CP(f_1,z_1)$ is the conditional power at the IA
- **Φ{.}** is the cumulative distribution function of a standard Normal distribution ($\mu=0$, $\sigma^2 = 1$)
- f_1 is the fraction of patients enrolled and used in the interim analysis before decision of increasing the sample size
- z_α is the upper α quintile for standard Normal distribution
- z_1 is the standardized Normal, since the primary endpoint is based on proportions the z-score will be obtained from the following formula:

$$z_1 = (P_s - P_p) / \sqrt{[P_p (1 - P_p) / n_p + P_s (1 - P_s) / n_s]}$$

Where:

- P_p = the number of events in group p ÷ the number of subjects in group p
- n_p = the number of subjects in group p used in the interim analysis
- P_s = the number of events group s, divided by number of subjects in group s
- n_s = the number of subjects in group s used in the interim analysis
- p = PMX Cartridge hemoperfusion plus SOC
- s = Sham hemoperfusion plus SOC

Rules for sample size increase: The sample size will be adjusted only if the CP is 50% or more and less than 80%. The sample size will be recalculated based on the observed event rates in both groups, i.e., Pp and Ps mentioned above.

If the trial is not stopped due to O'Brian-Fleming pre-determined alpha, (i.e., 0.005); then regardless of the size of the conditional power, the trial sample size of 360 will not be reduced. That is the sample size will be maintained as the original sample size, if the conditional power is larger than or equal to 80%. If the conditional power is less than 80%, the sample size will be increased to bring up the conditional power to 80%.

The maximum number of subjects that will be added to the trial enrollment number will not be larger than 360 subjects, i.e. the total trial is not in excess of 720.

7.7 Covariates and Prognostic Factors

No covariate analyses are planned.

7.8 Stratification Factors and Subgroups

The randomization for the study was stratified by site. This stratification is used to ensure a balanced distribution of subjects among the two treatment groups.

7.9 Standard Calculations

7.9.1 Age

Age will be calculated as the number of completed years between the date of informed consent and the subject's birth date.

Age (years) =
integer of [(date of informed consent for EAA – date of birth) / 365.25 + 0.5]

7.9.2 Treatment Duration

Subjects will receive 2 cartridges approximately 24 hours apart. There will be no re-treatments with the PMX cartridge after the completion of the 2nd cartridge. Treatment duration will be calculated for each treatment as the total number of minutes of treatment administration.

1st Cartridge Treatment Duration (mins) =
(First treatment stop time – First treatment start time)
2nd Cartridge Treatment Duration (mins) =
(Second treatment stop time – Second treatment start time)

7.9.3 Time to Any Event

The number of days from the randomization date to any event will be calculated as follows.

Time to Event (days) = (Date of Event – Date of randomization) + 1

7.9.4 Change in Endotoxin Level

The change from baseline endotoxin level to specified post baseline time points will be calculated as follows. All endotoxin levels will be those determined by EAA.

Change in Endotoxin Levels = Post-baseline endotoxin value – Baseline endotoxin value

7.9.5 *Changes in Cumulative Vasopressor Index (CVI)*

The change in cumulative vasopressor index (CVI) from Baseline (Day 0) to any post baseline time point is calculated using the following formula.

Change in CVI = Post-baseline CVI Score - Baseline CVI Score

7.9.6 *Change in Mean Arterial Pressure (MAP)*

The change in mean arterial blood pressure (MAP) from baseline (Day 0) to any post-baseline time point is calculated using the following formula.

Change in MAP (mmHg) = Post-baseline MAP value - Baseline MAP value

7.9.7 *Change in Renal Function as Assessed by Serum Creatinine*

The change in renal function, as assessed by serum creatinine (sCr), from baseline to 72 hours (Day 3) is calculated using the following formula.

Change in sCr (mg/dL) = 72-hr (Day 3) sCr value - baseline sCr
Note: For summary purposes, subjects on RRT will be assigned the max creatinine value (i.e. 4).

7.9.8 *Change in Renal Function as Assessed by Urinary Output*

The change in renal function, as assessed by Urinary Output (UO), from baseline to 72

hours (Day 3) is calculated using the following formula.

Change in UO (mL) =
72-hr (Day 3) UO value - baseline UO

7.9.9 *Change in Renal Function as Assessed by AKIN Score*

The change in renal function, as assessed by AKIN score, from baseline to any post-baseline time point is calculated using the following formula.

Change in AKIN =
Post-baseline AKIN score - Baseline AKIN score

7.9.10 Change in Organ Function as Assessed by the Multiple Organ Dysfunction Score (MODS)

The change in organ function, as assessed by MODS score, from baseline to 72 hours (Day 3) is calculated using the following formula.

Change in MODS =
Post-baseline MODS score - Baseline MODS score

7.9.11 Calculation of the PaO_2:FiO_2 Ratio

The PaO2:FiO2 ratio is calculated using the following formula.

PaO_2:FiO_2 Ratio =
PaO_2 value (mm Hg) / FiO_2 value (%) x 0.01*
*multiplying the FiO_2 % value by 0.01 converts the percent value to mm Hg

7.9.12 Change in Respiratory Function as Assessed by the PaO_2:FiO_2 Ratio

The change in respiratory function, as assessed by the PaO_2:FiO_2 ratio, baseline to 72 hours (Day 3), is calculated using the following formula.

Change in Respiratory Function =
72-hour (Day 3) PaO_2:FiO_2 Ratio score - baseline PaO_2:FiO_2 Ratio

7.9.13 Change in Hepatic Function as Assessed by Total Bilirubin

The change in hepatic function, as assessed by total bilirubin (mg/dL), baseline to 72 hours (Day 3), is calculated using the following formula.

Change in Hepatic Function =

72-hour (Day 3) total bilirubin value (mg/dL) - baseline total bilirubin value (mg/dL)

7.9.14 Change in Hematologic Function as Assessed by Platelet Counts

The change in hematologic function, as assessed by platelet counts (K/µL), from baseline to 72 hours (Day 3), is calculated using the following formula.

Change in Hematologic Function = 72-hour (Day 3) platelet count (K/µL) - baseline platelet count (K/µL)

7.9.15 Body Temperature

Temperature will be expressed in degrees centigrade, and entries made in degrees Fahrenheit will be converted to degrees centigrade using the formula noted below.

Temp (degrees centigrade) = $\left(\frac{5}{9}\right)$ * [temp (degrees Fahrenheit) - 32]

8. STUDY SUMMARIES

Due to the interim changes in the study Exclusion criteria (i.e., excluding subjects with a screening MOD score ≤ 9) and to address the potential impact of this change in the study design, the final analysis of efficacy results will be conducted using the following groups of subjects:

1. Only patients with a MOD score of > 9 enrolled post interim analysis (9April2014)
2. Only randomized subjects with a MOD score of > 9 from pre and post interim Analysis
3. All randomized subjects pre and post interim analysis combined

In addition, due to the nature of the trial (i.e., Primary endpoint at Day 28 with a 12 months long term follow up), the data for this study will be analyzed at two times: once when the primary endpoint data collection is complete (i.e. following the completion of Day 28) and once when all the long-term safety data collection is complete.

9. STATISTICAL METHODS

All data from this clinical trial will be provided in data listings by treatment group, clinical trial center, subject, and time point (if applicable).

9.1 Summarizing and Tabulating the Collected Data

All data collected will be summarized according to the variable type:

- Continuous data summaries will include:
  - Number of observations, mean, standard deviation, median, and minimum and maximum values.
  - Analysis of Covariance (ANCOVA) OR Mixed Model
- Categorical data summaries will include:
  - Frequency counts and percentages.
  - Fishers exact test or chi-square test will be used
- Time-dependent data: Kaplan Meier methods will be used to analyze time dependent data and to depict the time to event data.

9.1.1 Subject Disposition and Withdrawals

There will be a detailed accounting of all subjects who sign an informed consent to participate in this trial. The following will be summarized by treatment group:

- The number of subjects who signed informed consent for EAA
- The number of subjects who are screen failures
- The number of subjects who signed informed consent for randomization/treatment
- The number of subjects who are randomized
- The number of randomized subjects at each study site
- The number of randomized subject whose treatment was initiated
- The number of treated subjects completing through the Day 28 follow up.
- The number of subjects who completed the study, through the 12-month follow-up (Note: this summary will only be included in the follow up to the PMA submission)
- The number of subjects who withdrew and the reason for withdrawal will also be summarized as:
  - Screen failure (subjects who signed EAA consent but were not randomized)
  - Subject request

- Investigator request
- Pregnancy
- Withdrawal from the study due to adverse event(s)
- Subject did not receive treatment
- Significant protocol violation
- Death
- Other

In addition, the subject disposition will be presented as by-subject listings and a separate listing of screen failures and reason for screen failure will also be presented.

9.1.2 Protocol Deviations

The major deviations occurring during the clinical trial will be summarized descriptively according to the following categories for the subjects in the safety population:

- Inclusion/ Exclusion criteria not met but entered in the study
- Developed withdrawal criteria during the study but not withdrawn
- Study drug dosing deviation (Investigational product administration deviation). This major deviation will include (1) administration of the wrong treatment based on the randomization schedule or (2) if the start time of the first treatment administration is out-side the protocol-specified window or (3) if the start time of second treatment administration is greater than 12 hours outside the protocol-defined window for the second treatment administration.
- Received excluded concomitant medication

Additionally, a by-subject listing of all deviations will also be prepared.

9.1.3 Demographics

Demographics (age, race/ethnicity, gender, baseline body weight, baseline height) will be summarized descriptively and listed, by treatment groups for the Safety population. See Section 7.1 for baseline definition.

9.1.4 Baseline Characteristics

Baseline characteristics such as medical and surgical history results (coded using MedDRA version 14.1), EAA test results, information about the location of the subject prior to admission to Intensive Care Unit (ICU), primary reason for ICU admission,

reproductive status and pregnancy test (for female subjects), APACHE II score and baseline culture results will be summarized and/or listed, descriptively, by treatment groups for the Safety population.

9.1.5 Prior and Concomitant Medications

Prior and concomitant medications will be summarized for the Safety population. All prior and concomitant medications recorded in the case report form (CRF) will be coded to generic term and all matching Anatomic Therapeutic Classification (ATC) codes using WHO Drug version Y2011SEP. Summaries will be prepared using the coded pharmacological group and generic term. All prior and concomitant medications recorded in the CRF will be listed.

9.1.6 Surgical and Concomitant Treatments

Surgical and concomitant treatments will be summarized for the Safety population. All Surgical and concomitant treatments recorded in the case report form (CRF) will be classified by system organ class and preferred term (PT) according to MedDRA dictionary (Version 14.1). Summaries will be prepared using the system organ class and PT. All surgical and concomitant treatments recorded in the CRF will be listed.

9.1.7 Vasopressor Use

Vasopressor use will be summarized for the Safety population. All vasopressors recorded in the case report form (CRF) will be coded to generic term and all matching Anatomic Therapeutic Classification (ATC) codes using WHO Drug version Y2011SEP. Summaries will be prepared using the coded pharmacological group and generic term. All vasopressors recorded in the CRF will be listed.

9.1.8 Treatment Exposure

All the information recorded in the CRF regarding first treatment administration and second treatment administration will be presented as a by-subject listing and in addition treatment duration in hours will be summarized, descriptively, by treatment group for the Safety populations. See Section 7.9.2 for standard treatment duration calculation.

9.1.9 Accountability

All investigational device (PMX/ SHAM) accountability information recorded in the

CRF after each treatment will be presented as a by-subject listing.

9.2 Analysis of Efficacy Data

All statistical tests for efficacy will be two-sided tests.

The primary analysis of primary and secondary endpoints will be conducted on the ITT population who were randomized after 9April2014. Additionally, the PP population will be used as a supportive analysis if there is at least 5% difference between the numbers of subjects in the two populations.

9.2.1 Primary Endpoint

Mortality rate within 28 days after the initiation of the treatment perfusion or the sham perfusion is the primary endpoint for this study (see hypothesis in Section 4).

Fisher's Exact test will be used to test the primary endpoint if the number of events in any cell (of the contingency table) is less than 5; otherwise Chi-Square test will be used to analyze proportions of subjects who died within the 28 days after initiation of perfusion in the two treatment groups.

For this analysis subjects with unknown survival status will be excluded from the primary analysis. In addition, sensitivity analyses will also be performed to account for subjects with unknown survival status (i.e., two analyses will be performed:

1: all subjects with unknown survival status will be assumed to be dead at Study Day 28 and

2: all subjects with unknown survival status will be assumed to be alive at Study Day 28.

9.2.2 Secondary Endpoints

As discussed in Section 7.5, to protect the type I error rate for the secondary endpoints, the closed test procedure will be used. Discussed below are the approaches that will be taken for each of the secondary endpoints. These endpoints are presented in the order that will be tested.

9.2.2.1 Survival Time from Baseline to Death within 28 Days

Time to death from the initiation of the treatment perfusion or the sham perfusion to death within 28 days will be compared and depicted using Kaplan Meier product limit estimator (see Section 7.9.3 for time-to-death calculation).

The Log Rank test will be used to compare the survival time between the treatment groups.

For the subjects who are still alive after Day 28, their survival time will be treated as statistically censored at Day 28. For those subjects who drop out of the study or are lost to follow-up within 28 days of treatment initiation, their survival time will be treated as statistically censored at the time of their last follow-up visit.

In addition to the p-value, an asymptotic 95% confidence interval estimate to the difference of 28-day mortality rate between the two study arms will be obtained. Also the 95% confidence interval to the hazard ratio of death between the two study arms will also be obtained.

9.2.2.2 Change in Organ Dysfunction from Baseline to 72 hours (Day 3) as Assessed by the total Multiple Organ Dysfunction Score (MODS)

A general linear mixed effects model will be used to analyze the mean change in the total Multiple Organ Dysfunction Score (MODS) (Day 0, Day 1, and Day 2 and Day 3).

The model will contain:

- a fixed effect of the treatment groups (standard medical care alone vs. standard medical care plus the PMX cartridge)
- a fixed effect of time (Day 0, 1, 2 and 3, treated as a classification variable)
- interactive effects
- a random effect of the study sites

An unstructured covariance structure between repeatedly measured values within same subjects will be used in the model.

For this analysis, the primary interest will be the comparison of treatment groups on the mean change in the total Multiple Organ Dysfunction Score (MODS) between Day 0 and Day 3. Point estimates, as well as 95% confidence interval (CI) estimates to the mean difference of change in total MODS between Day 0 and Day 3, will be obtained for each

study group through appropriate contrasts. The efficacy comparison between the two study groups will be achieved by statistically testing the interactive effect between the treatment groups and the measurement times (restricted to Day 0 and Day 3) through an appropriate contrast based on the model. A 95% confidence interval (CI) estimate based on the model for the mean difference between the two treatment groups will also be computed to assess the magnitude of the group difference on the change in total MODS from Day 0 to Day 3.

In addition sensitivity analysis will also be performed using LOCF (i.e., for the change from Day 0 of total MODS at Day 3, Day 2 observation will be carried forward if Day 3 observation is missing) and this imputed data will be analyzed using general linear mixed effects model. This model will contain:

- a fixed effect of the treatment groups (standard medical care alone vs. standard medical care plus the PMX cartridge)
- a fixed effect of the baseline MOD score
- a random effect of the study sites.

Point estimates, as well as 95% confidence interval (CI) estimates to the adjusted mean change from the baseline, will be obtained for each treatment group. The efficacy comparison between the two treatment groups will be achieved by statistically testing the fixed effect of study groups based on the model. A 95% confidence interval (CI) estimate based on the model for the mean difference between the two study groups will also be computed to assess the magnitude of the group difference on the change in total MODS from Day 0 to Day 3. All tests and CIs involved in these analyses will be two-sided.

9.2.2.3 Change from Baseline to Day 3 in Mean Arterial Pressure (MAP)

A general linear mixed effects model using the SAS Mixed procedure will be used to compare the mean change in mean arterial pressure (MAP) at Day 3 from the mean baseline level for each study group. The analysis will be done using similar analytic and sensitivity approaches detailed in Section 9.2.2.2 (for the analysis of MODS).

9.2.2.4 Change in Renal Function from Baseline to 72 hours (Day 3), as Assessed by Urinary Output

A general linear mixed effects model using the SAS Mixed procedure will be used to

compare the mean change in urine volume between the treatment groups. The analysis will be done using similar analytic and sensitivity approaches detailed in Section 9.2.2.2 (for the analysis of MODS).

9.2.2.5 Change in Renal Function from Baseline to 72 hours (Day 3), as Assessed by Serum Creatinine Values

A general linear mixed effects model using the SAS Mixed procedure will be used to compare the mean change in serum creatinine levels between the treatment groups. The analysis will be done using similar analytic and sensitivity approaches detailed in Section 9.2.2.2 (for the analysis of MODS).

9.3 Analysis of Safety Data

The Safety population will be used for all analyses of safety. All safety parameters will be presented descriptively and as data listings.

In addition treatment group differences in safety will be assessed with t-test or Wilcoxon test for the continuous variables and Fisher's exact test for categorical variables, as necessary.

9.3.1 Adverse Events (AEs)

Adverse events will be classified by system organ class and preferred term (PT) according to MedDRA dictionary (Version 14.1).

All adverse events, that occur on or after the date of first treatment administration, will be listed and summarized using frequency counts and percentages, by treatment group.

- Overall (*i.e.,* regardless of severity or relationship to treatment)
- By severity CTCAE grade (mild, moderate, severe, life threatening, death)
- By relationship to clinical trial treatment (not related, remote, possible, probable, definite)

Unless otherwise specified, at each level of summarization, a subject will be counted only once. If there is more than one occurrence of an event, the event of the worst severity or the worst-case relationship category will be summarized.

AEs leading to premature discontinuation of investigational treatment and Serious

Adverse Events (SAEs) will also be summarized by treatment group and relationship.

Adverse Events leading to premature discontinuation of investigational treatment will be defined as any adverse event with an Action Taken on study treatment equal to "discontinuation of IP".

All adverse events recorded in the CRF will be presented as by-subject listings.

In addition, Adverse Device Effects (ADEs), Serious Adverse Device Effects (SDAEs) and Unanticipated Serious Adverse Device Effects (USDAEs) will also be presented as a by-subject listing.

9.3.2 Vital signs

Vital signs assessments are performed at baseline (Day 0), on treatment days 1, 2, 3, 7, 14, 21 and post treatment Day 28. The vital signs parameters include core temperature (^{o}C/ ^{o}F), heart rate (beats/min), systolic and diastolic blood pressure (mmHg), MAP (mmHg), RAP/CVP (mmHg), respiratory rate (breaths/ min), FiO2 (%), PaO2 (mmHg), and SaO2 (%).

Summary statistics of raw data and change from baseline values will be presented by visit for each vital sign parameter.

Summaries will include the number of observations, mean, standard deviation, median, and minimum and maximum values. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

9.3.3 Clinical Laboratory Evaluations

All available results of the clinical laboratory evaluations will be listed and summarized by treatment group. Laboratory evaluations include blood chemistry, hematology, coagulation parameters and urinalysis.

9.3.3.1 Laboratory Values over Time

Summary statistics of raw data and change from baseline values for each laboratory parameter will be presented by treatment group and time point. Data will be summarized as appropriate to the variable type.

1. For continuous data, summaries will include the number of observations, mean, standard deviation, median, and minimum and maximum values.

2. For categorical data, frequency counts and percentages will be used.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

9.3.3.2 Individual Subject Changes (Shift Tables)

Individual subject changes will be identified through shift tables. Shift tables will be presented for each laboratory parameter with counts and percentages of subjects, by treatment group and time point, for shift (change) from baseline, using the normal ranges.

9.3.3.3 Clinically Significant Abnormalities

A by-subject listing of treatment-emergent clinically significant laboratory values, by treatment group, will be prepared.

9.3.4 Electrocardiogram (ECGs)

ECG assessments are performed at baseline (Day 0) and post treatment Day 28. The ECG parameters include mean RR interval, mean PR interval, mean QRS interval, and mean QT interval.

9.3.4.1 ECG Values over Time

Descriptive statistics of raw data and change from baseline values for each ECG measurement will be presented by treatment group. For change from baseline summaries, subjects with an undefined change from baseline, because of missing baseline data, will be excluded.

9.3.4.2 Individual Subject Changes (Shift Tables)

Individual subject changes will be identified through shift tables. Shift tables will be presented for the ECG interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects, by treatment group, for shift (change) from baseline, using the normal ranges.

9.3.4.3 Clinically Significant Abnormalities

A by-subject listing of treatment-emergent clinically significant ECGs, by treatment group, will be prepared.

9.3.5 Physical Examination

Physical examination is performed at baseline (Day 0) and post treatment Day 28.

All physical examination findings will be listed by treatment group.

As all clinically significant abnormal physical examination findings that were treatment-emergent were recorded as adverse events, the summarizations of clinically significant physical exam findings are integrated with the adverse events summaries.

9.3.6 Overall morbidity, plus mortality

Subjects who die or who have a morbidity event (defined as organ dysfunction per the MOD Score and AKI Score) during the 28-day post treatment period will be listed and summarized using frequency counts and percentages, by treatment group.

9.3.7 Infection Summary

Infection summary assessments are performed at baseline (Day 0) and post treatment Day 28.

All findings of probable location of infection (as assessed by the principal investigator) and the evidence in support of the PI's assessment will be presented as a by-subject listing and will be summarized as necessary.

9.3.8 Microbiology culture results

All microbiology culture results will be presented as subject listings, by culture site and treatment group.

9.4 Exploratory Analyses

9.4.1 Change in Respiratory Function from Baseline to 72 hours (Day 3), as assessed by the pO2/FiO2 Ratio

Respiratory (PO2/FiO2) component of the MODS score is rated by a 0- 4 scale where the categories in the scale are:

0 = > 300 or NA
1 = 226 – 300
2 = 151 – 225
3 = 76 – 150
4 = ≤ 75

A general linear mixed effects model using the SAS Mixed procedure will be used to compare the change in pO2/FiO2 Ratio at Day 3. The analysis will be done using similar specifications detailed in Section 9.2.2.2.

9.4.2 Change in Hepatic Function from Baseline to 72 hours (Day 3), as assessed by Total Bilirubin Values

Hepatic (Total Bilirubin) component of the MODS score is rated by a 0- 4 scale where the categories in the scale are:

0 = < 1.2 or NA
1 = 1.2 – 3.5
2 = 3.6 – 7.0
3 = 7.1 – 14.0
4 = > 14.0

A general linear mixed effects model using the SAS Mixed procedure will be used to compare the change in Total Bilirubin at Day 3. The analysis will be done using similar specifications detailed in Section 9.2.2.2.

9.4.3 Change in Hematologic Function from Baseline to 72 hours (Day 3), as assessed by Platelet Counts

Hematologic (Platelets) component of the MODS score is rated by a 0- 4 scale where the categories in the scale are:

0 = > 120 or NA

1 = 81 - 120

2 = 51 - 80

3 = 21- 50

4 = ≤ 20

A general linear mixed effects model using the SAS Mixed procedure will be used to compare the change in platelet counts at Day 3. The analysis will be done using similar specifications detailed in Section 9.2.2.2.

9.4.4 Change in Kidney Function from Baseline to 72 hours (Day 3), as assessed by the Composite Acute Kidney Injury (AKI) Score

A general linear mixed effects model using the SAS Mixed procedure will be used to compare the change in AKI score at Day 3. The analysis will be done using similar specifications detailed in Section 9.2.2.2.

9.4.5 Changes in Cumulative Vasopressor Index (CVI) from baseline to 72 hours (Day 3)

A general linear mixed effects model using the SAS Mixed procedure will be used to compare the change in CVI at Day 3. The analysis will be done using similar specifications detailed in Section 9.2.2.2.

9.4.6 Comparison of the Number of Days Alive and Free of the Following from Day 0 through Day 28: Renal Replacement Therapy, Mechanical Ventilation, and Vasopressor Use

The need for renal replacement therapy (RRT) and mortality status will be assessed daily in a binary scale (RRT/Alive: yes or no) from Day 0 to Day 28. Days alive and free of RRT (within 28 days) since the initiation of the treatment perfusion or the sham perfusion will be compared using the Wilcoxon rank sum test.

The same procedure will be used for days alive and free of Mechanical Ventilation and Vasopressor Use.

9.4.7 Comparison of the Number of Days Spent in the Hospital by Subjects in each Group for Survivors to Day 28

The number of days spent in the hospital (derived as defined in 7.9.3) for the subgroup of subjects who survive to Day 28 will be compared between the two treatment groups.

Time from the initiation of the treatment perfusion or the sham perfusion to hospital discharge within 28 days will be compared and depicted using Kaplan Meier product limit estimator.

The Log Rank test will be used to compare the spent in the hospital between the treatment groups.

For this analysis subjects who drop out of the study or lost to follow up within 28 days OR those who are still in hospital after Day 28 will be statistically censored.

For these subjects who are still in hospital after Day 28, their survival time will be treated as statistically censored at Day 28. For those subjects who drop out of the study or are lost to follow-up within 28 days of treatment initiation will be censored using the time from treatment perfusion to the last known date they were in hospital.

9.4.8 Comparison of the Number of Days Spent in the Hospital by Subjects in each Group for Survivors to Day 90, Month 6 and Month 12

Similar analysis method as Section 9.4.7 will be used to determine number of days subjects spend in hospital will be used for the 90 day, 6 month and 12 month assessments.

9.4.9 Changes in Endotoxin Levels from Completion of 2nd Treatment through 12 hours after Completion of Treatment and from Completion of Treatment

through Day 7

Endotoxin levels will be measured by Endotoxin Activity Assay (EAA) to assess if two uses of the PMX cartridge decrease endotoxin levels.

A general linear mixed effects model using the SAS Mixed procedure will be used to compare the change in EAA at Day 3. The analysis will be done using similar specifications detailed in Section 9.2.2.2.

9.4.10 Exploratory Analyses of Study Population Subsets

The mortality rate at 28 days will be evaluated for the following subsets of subjects:

- subjects with a documented infection (any type)
- subjects with a documented Gram negative infection
- subjects with a documented Gram positive infection
- subjects with a documented mixed infection
- subjects with no documented infection
- subjects with a pulmonary (lung) infection (either suspected or documented)
- subjects with an infection other than pulmonary (either suspected or documented)
- subjects with baseline AKI score of 1 – 4, inclusive

The statistical method to be used for each of the subset analyses is provided in Section 9.2.1.

9.4.11 Survival Time from Baseline to Death within 90 Day, 6 Months, and 12 Months

The same analysis methodology described in Section 9.2.2.1 will be used to evaluate these survival times for the two treatments. (Note: these summaries will only be included in the follow up to the PMA submission.)

9.4.12 Mortality at 90 Days, 6 Months, and 12 Months

The same analysis methodology described in Section 9.2.1 will be used to evaluate the proportion of subjects who die within 28 days of initiation of treatment. (Note: these summaries will only be included in the follow up to the PMA submission.)

9.5 Modifications from the Statistical Section of the Protocol, Version 8.0

The following modifications are made from the statistical section of the protocol:

- **<u>Definition of Safety Population</u>**

In the Protocol the safety population is defined as all subjects who have signed informed consent for treatment randomization. The safety population in this SAP is defined as all subjects who have signed informed consent for treatment randomization and the treatment has, at least, been initiated.

- **Analysis Methodology for analysis of the endpoint, the need for renal replacement therapy (RRT)**

  In the protocol it is mentioned that this endpoint will be analyzed by a general linear mixed effects model containing the fixed effect of the treatment groups (standard medical care alone vs. standard medical care plus the PMX cartridge) and a random effect of the study sites. However, since the magnitude of the number of days alive and free of RRT varies from subject to subject and it is high likely that the data will not be normally distributed, hence in this SAP a non-parametric method is planned to be used to compare the group difference.

9.6 Change History

Changes incorporated into Version 2.0 of this document.

1. Primary Efficacy Analysis Population

Change: The ITT population (defined in SAP Version 1.0 Section 6.1 as: "all subjects that have been randomized to receive either PMX treatment or the sham treatment") was replaced with the mITT population (defined in SAP Version2.0 Section 6.1 as: "all subjects who have been randomized and have completed the first treatment administration and have at least one post-treatment vital signs assessment"). And, the mITT population was defined as the primary analysis population for all efficacy parameters. Finally, it is noted in SAP Version 2.0 Section 6.1 that "all cases where a subject is randomized but does not receive treatment will be identified and summarized by randomized treatment group; and the reason for not receiving the study intervention will be described.

Rationale: Given that the study subjects in this trial are from a critical care population, it is not inconceivable that randomized subjects may expire or be moved away from the critical care study team (for an emergency operation or procedure) before the study intervention is able to be initiated. Current FDA guidance defines the follow up period as "…that period of time after the intervention during which the study subjects are scheduled to be observed and evaluated." [1] We agree with this definition, as the subjects who receive the intervention is the population of paramount importance to the outcomes of this trial. We expect that the number of randomized subjects who fail to receive intervention will be low (i.e., <5%) and we are collecting mortality status on all randomized subjects, through 28 days after randomization. However, we believe the mITT population (i.e., randomized subjects who have completed at least one treatment

administration) is the correct population to use as the primary population for the primary analysis.

1Statistical Guidance for Clinical Trials of Non Diagnostic Medical Devices, The Division of Biostatistics, Office of Surveillance and Biometrics, Center for Devices and Radiological Health, U.S. Food and Drug Administration, January 1996

2. Major Protocol Deviations Pertaining to Study Intervention

Change: By inference, SAP Version 1.0 Section 8.1.2 included all deviations from protocol-specified administration times as major protocol deviations (i.e., "Study drug dosing deviation (Investigational product administration deviation"). In SAP Version 2.0 Section 8.1.2 the definition of a major dosing deviation was modified to include only the following: administration of the wrong treatment based on the randomization schedule or deviations in treatment administration start time, that are greater than 12 hours (i.e., for the second treatment) outside the protocol-defined window for treatment administration.

Rationale: After discussion with DSMB it was determined that small deviations in the protocol-specified intervention start times should not be categorized as major deviations. The deviation time limit was set to greater than 12 hours (i.e., for the second treatment), as lesser time frames would not jeopardize the safety of the subject or the integrity of the trial.

3. Minor editorial changes were made for clarity

Changes incorporated into Version 3.0 of this document.

1. **Mortality Follow Up at Day 28, Day 90, 6 Month and 12 Month timepoints**

Change: The mITT population (defined in SAP Version 2.0 Section 6.1 as: "all subjects that have been randomized and have completed the first treatment administration and have at least one post treatment vital signs assessment") was replaced with the ITT population (defined in SAP Version 3.0 Section 6.1 as: "all subjects that have been randomized to receive either PMX treatment or the sham treatment"). And, the ITT population was defined as the primary analysis population for all efficacy parameters.

Rationale: This is per the comment from FDA (dated July 15, 2013) on the review of SAP Version 2.0.

2. **Mortality Follow Up at Day 28, Day 90, 6 Month and 12 Month timepoints**

Change: It is clarified in the document that every effort will be made to obtain the mortality status for ALL randomized subjects at the 28-day, the 90-day, the 6-month, and 12-month timepoints, regardless of treatment disposition or withdrawal status. This change is reflected in Section 2.1 and 2.2.

Rationale: As discussed above, per the communication with the agency, the primary analysis population for the efficacy analysis will be ITT; hence, all effort will be made to obtain the mortality status for all ITT subjects to avoid unknown mortality status in the analysis population.

3. **Internet-based Randomization System**

Change: In the previous versions of the SAP the process for randomization was paper based in it was using sealed envelopes that would be sent to the study pharmacists; to

make this process more efficient a secure internet-based randomization system is developed and this change is reflected in Section 2.3.2 of this document.

Rationale: Web-based randomization is more efficient and less prone to errors. The system is always up to date and there is no need to wait until randomization forms are collected from site to know that subjects have been randomized and received the assigned treatment.

4. **Protocol Deviations**

Change: It is clarified in the document that dosing deviations are considered major:

1. if administration of the wrong treatment based the randomization schedule
2. if the start time of the first treatment administration is out-side the protocol specified window or
3. if the start time of the second treatment administration is greater than 12 hours outside the protocol defined window for the second treatment administration.

Rationale: Administration of study treatments within a few hours outside the designated window is not of concern, but longer delays could affect study results; hence, administration of study treatments at time points > 12 hours outside the protocol specified window is considered major protocol deviation.

5. **Minor editorial changes were made for clarity**

9.7 Change History

Changes incorporated into Version 4.0 of this document.

1. Sample size per the DSMB recommendation

Change: Added Section 3.2 to include the description of the new sample size recommendation.

Rationale: Due to the results of the Efficacy Interim Analysis and the recommendation from the DSMB, the sample size for the study is increased.

2. Planned analyses post-interim analysis changes

Change: Added section 8 detailing how the data collected from the study will be used for the final analysis.

Rationale: To address Item #1 of the FDA question on the 30May2014 letter.

3. Minor editorial changes were made for clarity and per Amendment 9.0 of the protocol.

9.8 Change History

Changes incorporated into Version 5.0 of this document.

1. Sample size per the FDA recommendation

Change: Added Section 3.3 to include the description of the new sample size recommendation.

Rationale: Due to the results of the Efficacy Interim Analysis and the recommendation from the FDA, the sample size for the study is changed.

2. Analysis populations

Change: Changed the analysis populations for the primary objective as the Intent to treat population to only include subjects randomized after 9April2014.

Rationale: To address Item #1 of FDA recommendation: "to determine the effect of your device on patients with a MOD score of > 9, analysis of effectiveness should be based only on patients enrolled after the new exclusion criterion was enacted for each study site. We recommend you revise your analysis plan accordingly." on the 30 May 2014 letter.

3. Study summaries

Change: Added the summary item 4 to summarize subjects randomized after 9April2014.

Rationale: To address Item #1 of FDA recommendation: "to determine the effect of your device on patients with a MOD score of > 9, analysis of effectiveness should be based only on patients enrolled after the new exclusion criterion was enacted for each study site. We recommend you revise your analysis plan accordingly." on the 30May2014 letter.

4. Analysis of efficacy data

Change: Changed the analysis populations including Intent to treat population to only include subjects randomized after 9April2014.

Rationale: To address Item #1 of FDA recommendation: "to determine the effect of your device on patients with a MOD score of > 9, analysis of effectiveness should be based only on patients enrolled after the new exclusion criterion was enacted for each study site. We recommend you revise your analysis plan accordingly." on the 30 May 2014 letter.

9.9 Change History

Changes incorporated into Version 6.0 of this document.

1. Secondary and Exploratory endpoints adjustments

Change: Rearranged the order of secondary and exploratory endpoints within the framework of the Closed Test Procedure Analytical method

Rationale: The first criterion remains as in the previous version, that is, survival time to 28 days. Then, whereas sponsor initially believed that a composite organ dysfunction score (MODS) was next in importance; sponsor now believe that organ specific measures provide more precise information of the possible effects of removal of endotoxin. Published evidence from literature of PMX use, [EUPHAS study and Cruz Meta-

analysis] show that change in composite organ dysfunction criteria is mainly driven by changes in the cardiovascular and renal organ systems.

To reflect the change in cardiovascular system over time, it is proposed that the use of the Cumulative Vasopressor Index (CVI) as changes in vasopressor needs reflect improvement or lack of improvement of cardiovascular function more precisely than changes in Mean Arterial Pressure (MAP). For the renal effects of endotoxin removal, creatinine values are considered as more reliable than urine output as a marker of kidney function over time.

In summary, organ function criteria is consistently considered as important secondary endpoints following mortality in the evaluation of the efficacy of the PMX cartridge yet the ranking was changed from composite score followed by organ specific values to the organ specific criteria and then the composite organ dysfunction score. All remaining criteria within the SAP are exploratory endpoints.

2. Sample size recalculation

Change: Changed the sample size based on changed attrition rate

Rationale: Since actual dropout is very small sponsor decided to recalculate the sample size with the 2% dropout rate.

3. Treatment duration calculation

Change: The treatment duration will be calculated for each treatment session separately instead of combined

Rationale: Since there are two treatment sessions, the duration will be calculated separately.

4. Renal Function as Assessment

Change: Added a note regarding how to calculate creatinine value for subjects on RRT

Rationale: Due to clinical judgment, subjects on RRT will be assigned the max creatinine value.

5. Study summaries

Change: The analyses are to be conducted at two times: once when the primary endpoint data collection is complete (i.e. following the completion of Day 28) and once when all the long-term safety data collection is complete

Rationale: Due to the nature of the trial (i.e., Primary endpoint at Day 28 with a 12 months long term follow up).

9.10 Change History

Changes incorporated into Version 7.0 of this document.

1. Secondary and Exploratory endpoints adjustments

Change: Rejected the changes on secondary and exploratory endpoints in version 6.0

Rationale: Due to the recommendation from the FDA on March 10th 2016, the secondary and exploratory endpoints were kept the same as before.

2. Sample size recalculation rationale

Change: Rejected the changes on Section 3.3 sample size recalculation rationale.

10. REFERENCES

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5. Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3), July 1996.
6. Christopher Jennison, and Bruce W. Turnbull. Chapter 2 (section 2.5) in Group Sequential Methods with Applications to Clinical Trials
7. O'Brien PC, Fleming TR. (1979). A multiple testing procedure for clinical trials. Biometrics 35:549-556
8. Chen JYH, Demets DL, and Lan KKG ‘ Increasing the Sample Size when unblinded interim results is promising,’ Statistics in Medicine 23 (2004) 1023- 1038.
9. Amarex. Interim Analysis and DSMC Preparation Standard Operating Procedure (SOP BM007 v9, March 1, 2012), Amarex LLC, Germantown, MD.
10. Hung HMJ, Wang SJ, O’Neill R. (2007). Statistical considerations for testing multiple endpoints in group sequential or adaptive clinical trials. J of Biopharm Statistics. 17:1201-1210.

APPENDIX 1: PLANNED LISTINGS AND SUMMARY TABLES

Planned by-subject listings
The by-subject listings for the study will include the following information.

- DISPOSITION/WITHDRAWALS (LISTINGS 16.2.1.X)
- ELIGIBILITY AND PROTOCOL DEVIATIONS (LISTINGS 16.2.2.X)
- EXCLUDED SUBJECTS (LISTINGS 16.2.3.X)
- DEMOGRAPHICS, POPULATION, AND BASELINE CHARACTERISTICS (LISTINGS 16.2.4.X)
- DRUG COMPLIANCE AND DRUG CONCENTRATION LISTINGS (LISTINGS 16.2.5.X)
- EFFICACY RESPONSE DATA (LISTINGS 16.2.6.X)
- ADVERSE EVENT DATA (LISTINGS 16.2.7.X)
- SAFETY DATA (LISTINGS 16.2.8.1.X)
- OTHER SAFETY DATA (LISTINGS 16.2.8.2.X)

Planned Summary Tables
The summary tables for the study will include the following information.

- POPULATION DISPOSITION AND PROTOCOL DEVIATIONS
- POPULATION DEMOGRAPHICS AND BASELINE CHARACTERISTICS
- CONCOMITANT MEDICATION USAGE
- EXPOSURE DURATION
- EFFICACY SUMMARIES
- SAFETY SUMMARIES
    - ADVERSE EVENT SUMMARIES
    - SERIOUS ADVERSE EVENTS
    - LABORATORY
    - VITAL SIGNS
    - PHYSICAL EXAMINATION
    - OTHER SAFETY