# PHASE 3 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE SAFETY AND EFFICACY OF RELTECIMOD AS COMPARED TO PLACEBO IN ADDITION TO STANDARD OF CARE IN PATIENTS WITH SEPSIS-ASSOCIATED ACUTE KIDNEY INJURY (SA-AKI)

**Product**: Reltecimod

**Protocol Number**: ATB-203

**Development Phase**: Phase 3

**IND Number:** 128927

**EudraCT Number:** 2018-002547-29

**SPONSOR:** Atox Bio Ltd.
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Version 1.0 Protocol (USA) / Approval Date 22 January 2016
Version 2.0 Protocol (USA) / Approval Date 10 December 2017
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Version 4.0 Protocol (France) / Approval Date 27 September 2018
Version 5.0 Protocol (Global) / Approval Date 03 January 2019
Version 6.0 Protocol (Global) / Approval Date 31 July 2019

This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonization (ICH); United States (US) Code of Federal Regulations (CFR) and European Union (EU) Directives (as applicable in the region of the study); local country regulations; and the Sponsor's Standard Operating Procedures (SOPs).

## Signature Page

The signature below constitutes approval of this protocol by the signatory on behalf of Atox Bio, Ltd.

Atox Bio, Ltd (Atox Bio) agrees that it will arrange for the supply of the clinical study drug (investigational medicinal products [IMP]) described in this protocol and undertakes to report adverse events to the relevant authorities in compliance with the regulations. It further agrees to inform the Investigators of any information that would place the patients at risk by their continuing participation in the study.

## Sponsor Representatives

Wayne M Dankner

31JUL2019

Wayne M Dankner, MD
Chief Medical Officer
Atox Bio, Ltd.

Date

1 August 2019

Michele LaRussa
Senior VP Regulatory
Atox Bio, Ltd.

Date

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## INVESTIGATOR AGREEMENT

Version 6.0 Approval Date 31 July 2019

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein, in compliance with current Good Clinical Practice (GCP) and the applicable regulatory requirements and will make every reasonable effort to complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals under my responsibility who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the IMP and the conduct of the study.

I will use only the informed consent form (ICF) approved by Atox Bio Ltd. ("Atox Bio") and/or its representative and the Institutional Review Board/Independent Ethics Committee ("IRB/IEC") and will fulfill all responsibilities for submitting pertinent information to the IRB/IEC responsible for this study.

I agree that Atox Bio, its representatives, or regulatory authorities shall have access to any source documents from which case report form information may have been generated. I agree to maintain in a safe and secure location all required study documents and primary source documents until notified by Atox Bio that such documents may by discarded or transferred.

I further agree not to originate or use the name of Atox Bio, or any of its employees, and/or Reltecimod in any scientific publication, marketing or publicity material, news release or other public announcement, written or oral, whether to the public, press or otherwise, relating to this protocol, to any amendment hereto, or to the performance here under, without the prior written consent of Atox Bio. I further agree to keep in confidence and not disclose any confidential information provided by Atox Bio and/or related to the study or Reltecimod.

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| **Investigator's Signature** | **Date** |

**Name of Investigator**

**Investigator Title**

**Institution, Address***

**Institution, Phone Number***

* If the address or phone number is changed during the course of the study, the Investigator will complete and provide a Form FDA 1572 to Atox Bio or its representatives but will not require a protocol amendment(s). Should the Investigator plan to retire or transfer to another institution, he/she shall notify the Sponsor and arrange for the transfer of responsibility for all retained study materials and source records.

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## 2. PROTOCOL SYNOPSIS

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| **Protocol Number** | ATB-203 |
| **Protocol Title** | Phase 3 randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of Reltecimod as compared to placebo in addition to standard of care in patients with sepsis-associated acute kidney injury (SA-AKI) |
| **Location(s)** | A multicenter study to be conducted in up to 90 qualified participating sites globally |
| **Phase of Development** | Phase 3 |
| **Study Population** | Patients with<br>• Suspected or confirmed abdominal infection (planned or completed surgical (laparotomy or laparoscopy) or interventional radiologic procedures for control of underlying abdominal infection within 24 hours of evaluation by medical personnel); or surgically confirmed necrotizing soft tissue infection (NSTI),<br>• Requiring hospital admission to an intensive care unit (ICU) or step-down unit (or equivalent),<br>• Total Sequential Organ Failure Assessment (SOFA) score $\geq$2, and<br>• In whom the diagnosis of Stage 2 or 3 acute kidney injury (AKI; as defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria) is established at initial presentation for medical evaluation; or up to 48 hours from the suspected or confirmed diagnosis of abdominal infection or surgical confirmation of NSTI. |

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| **Study Objectives** | **Primary Objective**<br>• To compare the rates of achieving the primary endpoint of freedom from durable loss of renal function (defined as alive, free of dialysis, and less than a 37% loss of estimated Glomerular Filtration Rate (eGFR; measured with the Modification of Diet in Renal Disease (MDRD) formula from the patient's reference eGFR)) at Day 28 between the Reltecimod- and placebo-treated patients<br>• To demonstrate the safety and tolerance of Reltecimod when administered as a single dose of 0.50 mg/kg to patients diagnosed with SA-AKI<br>**Secondary Objectives**<br>• To compare the rates of the primary endpoint at Day 14 between the Reltecimod- and placebo-treated patients<br>• To compare time to the primary endpoint between the Reltecimod- and placebo-treated patients<br>• To compare AKI-free days over 14 and 28 days between the Reltecimod- and placebo-treated patients<br>• To compare the resolution of organ dysfunction (organ resolution is defined as having a SOFA score of ≤1 at Day 14, for individual organs and for the total SOFA score) between the Reltecimod- and placebo-treated patients over time and at Day 14<br>• To evaluate the effect of Reltecimod (compared to placebo) in relation to the critical care and hospital stay parameters in patients with sepsis and AKI<br>o Hospital length of stay<br>o ICU length of stay<br>o ICU free days in 28 days<br>o Ventilator days<br>o Ventilator free days in 28 days<br>o Vasopressor days<br>o Vasopressor free days in 28 days<br>o Renal Replacement Therapy free days (days alive and free of RRT) in 28 days<br>• To compare survival status at Days 14 and 28 between the Reltecimod- and placebo-treated patients<br>• To tabulate the incidence of Stages 1, 2 and 3 AKI (using the KDIGO criteria) in patients with abdominal sepsis or NSTI<br>• To demonstrate the safety of Reltecimod in regard to susceptibility to secondary infections<br>**Exploratory Objectives**<br>• To compare the primary endpoint at Day 90 between the Reltecimod- and placebo-treated patients<br>• To compare the rates of improvement in durable loss of renal function (defined as alive, free of dialysis, and improvement leading to a lower AKI stage but no better than Stage 1 AKI) at Days 14, 28 and 90, between the Reltecimod- and placebo-treated patients |

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| | • To compare the distributions of acute kidney disease (AKD) stages (AKD 0, 1, 2, 3, and 3F) at Days 14 and 28 between the Reltecimod- and placebo-treated patients<br>• To conduct an exploratory evaluation of the incidence of chronic kidney disease (CKD) at Day 90<br>• To conduct an exploratory evaluation of survival status at Day 90 in the Reltecimod- and placebo-treated patients<br>• To conduct an exploratory evaluation of the primary endpoint by baseline pathogen<br>• To conduct an exploratory evaluation of RRT use (i.e., type of RRT)<br>• To evaluate the immunogenicity of Reltecimod<br>• To conduct an exploratory evaluation of plasma and urinary biomarkers in patients with AKI<br>• To conduct an exploratory evaluation of blood leukocyte transcriptome (RNA expression) profiling in patients with SA-AKI and compare genomic profile in patients treated with Reltecimod versus placebo<br>• To define potential surrogate biomarkers (systemic) that exhibit change from baseline due to treatment with Reltecimod |
| **Study Hypothesis** | The primary hypothesis of this study is that in addition to standard of care (SoC), the probability of meeting the primary endpoint of freedom from durable loss of kidney function (defined as alive, free of dialysis, and less than a 37% loss of eGFR (measured with the MDRD formula from the patient's reference eGFR)) at Day 28 will be higher among Reltecimod-treated patients compared to placebo-treated patients. |
| **Number of Patients:** | 120 patients with SA-AKI, due to an abdominal infection or NSTI, will be recruited into the study and randomized to receive either 0.50 mg/kg Reltecimod or placebo in a 1:1 ratio. Randomization will be performed within site and stratified according to acuity of AKI (i.e., whether or not AKI is diagnosed at time of presentation of abdominal infection or surgically confirmed NSTI; or during the 48 hours post-diagnosis of abdominal infection or surgical confirmation of NSTI) and subject age at time of enrolling in the study ($\geq$18 to $\leq$75 or >75 to $\leq$85 years old).<br>Overall, the study is expected to last approximately 36 months (from first patient in to last patient out). The study design includes plans for an interim analysis for the purpose of sample size re-estimation based on conditional power. The enrollment period may be longer than 36 months if a sample size expansion occurs. |

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| **Inclusion Criteria:** | 1. Age: 18 up to and including 85 years.<br><br>2. Has either suspected or confirmed diagnosis of abdominal infection with planned or completed surgical (laparotomy or laparoscopy) or interventional radiologic procedures within 24 hours of evaluation by medical personnel, or surgically confirmed NSTI, requiring treatment with parenteral antibiotics. Recommended surgical or interventional radiologic procedures for abdominal infection be performed with 12 hours of evaluation by medical personnel.<br><br>A. Abdominal Infection<br>• Suspected clinical diagnosis of abdominal infection as evaluated by the attending surgeon including any of the following clinical criteria<br>- Abdominal pain and/or tenderness<br>- Localized or diffuse abdominal wall rigidity<br>- Mass<br>- Ileus<br><br>AND<br><br>- Any of the following radiologic findings<br>▪ Free air (plain film, CT or MRI scans)<br>▪ Intraabdominal abscess (ultrasound, CT or MRI scans)<br>▪ Free peritoneal fluid (ultrasound, CT or MRI scans)<br><br>OR<br>• Confirmed diagnosis of abdominal infection by any of the of the following criteria<br>- Perforation and/or necrotic bowel with surgical confirmation of peritonitis<br>- Presence of intraabdominal abscess by surgical confirmation or drainage of purulent fluid from interventional radiologic procedure<br><br>OR<br><br>B. Necrotizing Soft Tissue Infection<br>• Surgical confirmation of NSTI by attending surgeon (e.g., presence of necrotic tissue, thrombosed vessels in the subcutaneous tissue, lack of bleeding and “dishwater” (cloudy, thin, gray) fluid due to presumed bacterial infection (necrotizing cellulitis (most commonly group A strep), necrotizing fasciitis, necrotizing myositis and myonecrosis, NSTI of the perineum, bacterial synergistic gangrene, Clostridial gas gangrene) that may be supported by specific signs and symptoms (e.g., tense edema outside area of compromised skin, pain disproportionate to appearance, skin discoloration, ecchymosis, blisters/bullae, necrosis, crepitus, and or subcutaneous gas).<br><br>3. SOFA score $\geq$2 (in any one or combination of the 6 major components of the SOFA score), measured as close as possible to study drug administration (but before study drug is administered).<br><br>4. Planned or current admission to an ICU or step down unit (or equivalent). |

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| | 5. Initial diagnosis of AKI established either upon presentation to medical care at the study site in those patients with suspected or confirmed abdominal infection or surgically confirmed NSTI; or in those patients in whom the initial diagnosis of AKI is established during the 48-hour period from the suspected or confirmed diagnosis of abdominal infection or surgical confirmation of NSTI.<br><br>AKI Stage 2 or 3 according to the following KDIGO AKI criteria<br><br>• Stage 2 AKI<br>- Increase in serum creatinine to ≥ 200% (≥ 2.0–fold) from a reference creatinine value (see below) in the absence of primary underlying renal disease (eGFR >30 mL/min)<br><br>OR<br><br>- Urine output < 0.5 mL/kg/hr x 12 hours following adequate fluid resuscitation [the aggregate over any 12-hour period can be used with hourly rate being relatively persistent over the 12-hour period]<br><br>Note: Urine output should be calculated using Ideal Body Weight (IBW; using the Miller Formula[52])<br><br>• Stage 3 AKI<br>- Increase in serum creatinine to ≥ 300% (≥ 3.0–fold) from a reference creatinine value in the absence of primary underlying renal disease (eGFR >30 mL/min)<br><br>OR<br><br>- Serum creatinine ≥4 mg/dL<br><br>OR<br><br>- Planned or initiation of RRT for acute AKI<br>▪ Order for RRT must be in place<br>▪ RRT may be started prior to study drug administration as long as the patient is off RRT during study drug administration and at least one hour post study drug administration<br><br>OR<br><br>- Urine output < 0.3 ml/kg/hr x 24 hours or anuria x 12 hours following adequate fluid resuscitation<br>▪ Urine output should be calculated using IBW (using the Miller Formula)<br><br>The reference creatinine value is the serum creatinine value according to the following order<br><br>- Value within 3 months of the hospital admission<br>- If single value available, then use the single value for reference<br>- If two values available, then use the average of two values for reference<br>- If three or more values available, then use the median of the three most recent values for reference<br>- Value between 3 and 12 months prior to hospital admission |

- If single value available, then use the single value for reference
- If two values available, then use the average of two values for reference
- If three or more values available, then use the median of the three most recent values for reference

- At hospital admission (if the patient is admitted without an acute illness)

- Patients without a reference creatinine value would also be considered to have Stage 2 or 3 AKI if they have a serum creatinine ≥ 200% (≥ 2.0-fold) the normal creatinine value for age, race, and gender (Appendix F) and a renal ultrasound (US) or computed tomography (CT) showing normal kidney size within the past 90 days. Normal kidney size is defined as
  - Computed Tomographic Scan
    - If either kidney is ≥9 cm length
  - Renal Ultrasound[54]
    - <60 years if either kidney is ≥10 cm length
    - ≥60 years if either kidney is ≥9.5 cm length

6. Study medication must be administered within 6 hours of confirmation of onset of Stage 2 or 3 AKI as established at the study site, under the following criteria
   - After the decision is made by the attending surgeon at the study site for a surgical or interventional radiology procedure for the abdominal infection

     OR
   - After confirmed diagnosis of abdominal infection has been established by a surgical or interventional radiology procedure

     OR
   - After surgical confirmation of NSTI
7. Females of childbearing potential must consistently use an acceptable method of contraception from baseline through Day 28. Females of childbearing potential must have a negative β-subunit hCG pregnancy test (urine or blood whichever is faster; blood only in France) immediately prior to study entry.
   - Non-childbearing potential is defined as current tubal ligation, hysterectomy, or ovariectomy or post-menopause (1 year without menses with an appropriate clinical profile at the appropriate age e.g. >45 years).
   - Acceptable methods of contraception for this study is defined as abstinence, hormonal therapy (e.g., oral contraceptives, hormone implants), intra-uterine (IUD) device, diaphragm with spermicide, condom with spermicide.
8. If a male patient's sexual partner is of childbearing potential, the male patient must acknowledge that they will consistently use an acceptable method of contraception (defined above) from baseline through Day 28.

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| | 9. Signed and dated informed consent form (ICF) as defined by the institutional review board (IRB) or Ethics Committee (EC) and, if applicable, California Bill of Rights. By signing the ICF, the patient agrees to release any medical records pursuant to current Health Insurance Portability and Accountability Act (HIPAA) Guidelines or to local country privacy regulations. If patient is unable to comprehend or sign the ICF, patient's legally acceptable representative (or an independent physician if allowed by local rules and regulations) may sign the ICF. |

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| **Exclusion Criteria:** | 1. Has known prior history of CKD with a documented eGFR < 30 mL/min by a commonly used formula such as MDRD or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), or known GFR < 30 mL/min.<br>• Exception: Patients with history of CKD but no available prior eGFR who have documented normal kidney size on ultrasound or computed tomography (normal size defined above) evaluation (performed within 90 days of screening) will be eligible<br><br>2. Patients receiving RRT for chronic kidney disease: either hemodialysis, peritoneal dialysis, hemofiltration such as Continuous Veno-Venous Hemofiltration (CVVH) or hemodiafiltration.<br><br>3. Previously diagnosed with documented AKI in the last 30 days.<br><br>4. Documented primary glomerular disease or toxic tubulo-interstitial nephritis or other underlying renal diseases significantly effecting renal function (e.g., renal amyloidosis, polycystic kidney disease, renal cancer, renal abscess) at the time of AKI diagnosis.<br><br>5. Patients with overt peripheral vascular disease in the involved NSTI area - associated with ischemic wounds/ulcers or gangrene, and/or other significant symptoms of inadequate vascular supply or where limb amputation is considered likely within 7 days due to the peripheral vascular disease.<br><br>6. Diabetic patients with peripheral vascular disease who present with below the ankle NSTI.<br><br>7. Current condition of<br>(a) Inability to maintain a mean arterial pressure > 50 mmHg and/or systolic blood pressure > 70 mmHg for at least 1 hour prior to dosing despite the presence of vasopressors and IV fluids or,<br>(b) a patient with respiratory failure such that an $SaO_2$ of 80% for at least 1 hour prior to dosing cannot be achieved, or<br>(c) a patient with refractory coagulopathy (INR >5) or thrombocytopenia (platelet count <20,000) that does not partially correct for at least 1 hour prior to dosing with administration of appropriate factors or blood products.<br><br>8. Severe neurological impairment due to cerebrovascular accident or cardiac arrest.<br><br>9. Recent cerebrovascular accident in the last 3 months.<br><br>10. Patients with cardiac arrest requiring cardiopulmonary resuscitation within the past 30 days.<br><br>11. Patient is not expected to survive throughout 28 days of study due to underlying medical condition, such as poorly controlled neoplasm (e.g. Stage III or IV cancer).<br><br>12. Classified as “Do Not Resuscitate”, or “Do Not Treat”, or the patient’s family is not committed to aggressive management of the patient’s condition. A “no |

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| | cardiopulmonary resuscitation (CPR)" order is acceptable if the patient and/or the family are still committed to aggressive care short of CPR.<br><br>13. Any concurrent medical condition, which in the opinion of the Investigator, may compromise the safety of the patient or the objectives of the study or the patient will not benefit from treatment such as<br>• Congestive heart failure (CHF) {New York Heart Association (NYHA) class III-IV}<br>• Very severe chronic obstructive pulmonary disease (COPD) {GOLD Stage IV or use of continuous home oxygen prior to hospital admission (sleep apnoea treated with continuous positive airway pressure or biphasic positive airway pressure oxygen during sleep is acceptable)}<br>• Liver dysfunction {Childs-Pugh class C}<br>• Primary or acquired immunodeficiency or immunosuppression due to treatment with immunosuppressive medications (see Appendix G for list of excluded immunosuppressive medications)<br>• Known HIV infection with CD4 count < 200 cells/$mm^3$ or < 14% of all lymphocytes<br>• Neutropenia < 1,000 cells/$mm^3$ not due to the underlying infection<br>• Receiving or about to receive chemotherapy or biologic anti-cancer treatment, although hormonal manipulation therapies for breast and prostate malignancies are permitted<br>• Hematological and lymphatic malignancies in the last 5 years<br><br>14. Patient with >20% body surface area burn wounds.<br><br>15. Patient has acute pancreatitis with no established source of infection, uncomplicated appendicitis, or cholangitis or cholecystitis without peritonitis. Note - necrotic or gangrenous gallbladder or appendix with peritonitis is allowed.<br><br>16. Pregnant or breastfeeding women (lactating women must not breastfeed and must discard breastmilk for at least 28 days after receiving study drug); Women of childbearing potential must have a negative β-subunit hCG pregnancy test immediately prior to study entry.<br><br>17. Previous enrollment in a clinical trial involving investigational drug or a medical device within 30 days before provision of written informed consent for the study or within five half-lives of the investigational drug, whichever is longer.<br><br>18. Previous enrollment in any Reltecimod protocol (ATB-001, ATB-201, ATB-202 or ATB-203).<br><br>19. Patients under guardianship or trusteeship (France only).<br><br>20. Absence of social insurance (France only). |

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| **Investigational Product: Type, Dose and Mode of Administration** | Reltecimod is the sodium acetate salt of a 10-amino acids synthetic peptide that is homologous to specific amino acid residues of the T-lymphocyte receptor CD28.<br><br>Reltecimod is packaged in glass vials as a lyophilized powder to be reconstituted with 10.5 mL of sterile water for injection (WFI) to a concentration of 1 mg/mL. Each vial contains 10.5 mg of Reltecimod with an excipient to protect the peptide during the lyophilization process. Sterile WFI should be obtained by the site pharmacy.<br><br>The dose of Reltecimod will be 0.50 mg/kg, administered as a one-time dose, with drug administration initiated within the 6-hour time-window from the diagnosis of SA-AKI, only after the decision is made by the attending surgeon at the study site for a surgical or interventional radiology procedure for the abdominal infection or after confirmed diagnosis of abdominal infection has been established by a surgical or interventional radiology procedure; or after surgical confirmation of NSTI as described in the inclusion criteria.<br><br>Drug will be reconstituted on the day of its administration, in close proximity to infusion time, and several vials will be pooled together to compose the requested dose. Drug will be administered as an intravenous infusion, separate from other medications, over 10 minutes using a syringe pump (may be manually pushed if approved by the medical monitor). Volume of administration will be dependent on the patients' actual weight plus adequate priming volume of the IV line.<br><br>Placebo for Reltecimod is pyrogen-free and preservative-free sterile 0.9% sodium chloride solution, USP. This should be obtained by the local pharmacy. The volume of blinded placebo should be calculated similarly as for the active group according to the patient's actual body weight (0.50 mL/kg), plus adequate priming volume of the IV line. |

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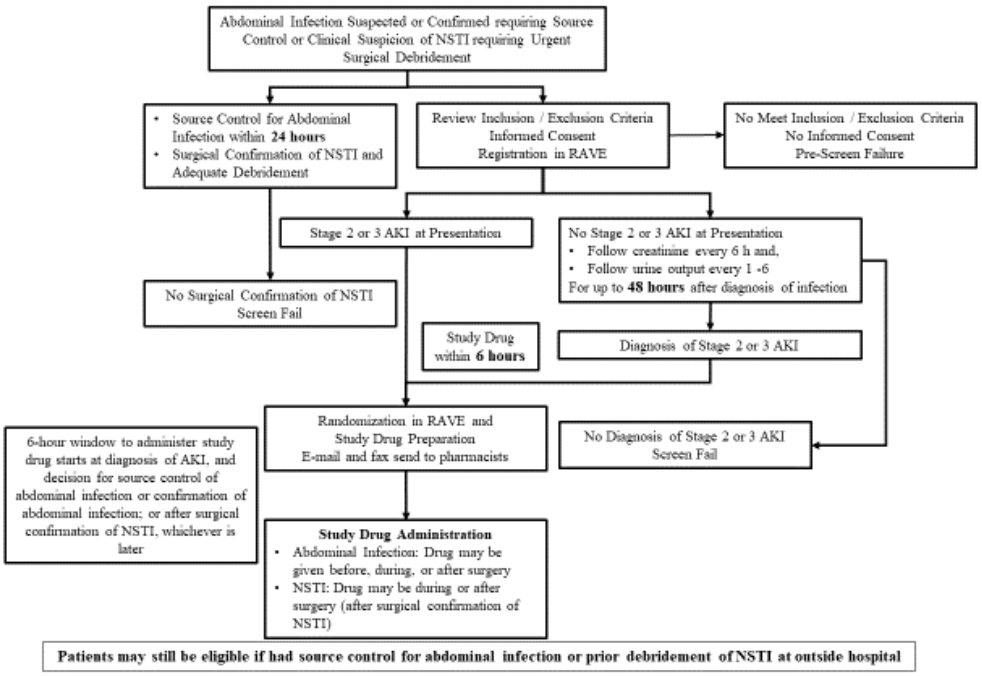
| **Flow Chart** | **Study design from clinical presentation to study drug administration for patients with abdominal infection or necrotizing soft tissue infection and confirmed Stage 2 or 3 AKI.** |



**Study Visits**

| Visit | Study Day |
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| 1 | Screening |
| 2 | Day 1<br>Begins with study drug administration and ends with the same calendar day |
| 3 | Day 2 |
| 4 | Day 3 |
| 5 | Day 7 (±1 day) |
| 6 | Day 10 (±1 day)<br>Perform only if patient is still hospitalized |
| 7 | Day 14 (±1 day) |
| 8 | Day 21 (±1 day) |
| 9 | Day 29 (+3 days) |
| 10 | 3 to 21 Days after Visit 9 |
| 11 | Day 90 (+5 days) Follow up & Termination |

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| | **SOFA Score Definition:**<br><br>Screening SOFA<br><br>Screening SOFA score components are to be captured and the total score to be calculated prospectively and must be performed prior to study drug administration. The SOFA score should be evaluated any time after arrival at the hospital (may include referring hospital evaluations), although should be no more than 6 hours prior to study drug administration. Total screening SOFA score must be ≥2 to be considered eligible for enrollment.<br><br>Sites are encouraged to re-evaluate the SOFA score as close to study drug administration as feasible for patients not meeting SOFA ≥2 inclusion criteria during initial screening.<br><br>Screening SOFA will include measurements of the components in the following organ/systems: respiratory (to include evaluation of oxygenation either directly by arterial blood gas or by calculation of PaO2 from SpO2), cardiovascular, renal, coagulation, GI/hepatic, and CNS.<br><br>SOFA Score<br><br>Measurements of 6 organ systems, including CNS. To be measured on Days 1, 3, 7, and 14 and calculated retrospectively.<br><br>SOFA Respiratory Parameter<br><br>In case it is not possible to take arterial blood gases to determine the SOFA respiratory parameter, SpO2/FiO2 ratio can be imputed for PaO2/FiO2 ratio. |

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| **Statistical Analysis** | **Randomization:** 120 patients will be recruited into the study and randomized to either 0.50 mg/kg Reltecimod or placebo in a 1:1 ratio. Randomization will be performed within site and according to two stratification variables.<br>• **Acuity of AKI:** whether or not AKI is diagnosed at time of presentation of abdominal infection or surgical confirmation of NSTI; or during the 48 hours following the suspected diagnosis of abdominal infection or surgical confirmation of NSTI.<br>• **Subject Age:** ≥18 to ≤75 or >75 to ≤85 years old.<br>Four computer generated, blocked randomization lists will be provided for each site, one for each of four strata defined on the basis of the 2 by 2 cross-tabulation of the two stratification variables. Within each block, half of the assignments will be to active drug and half to placebo, in random order. Block sizes will be varied.<br>**Blinding:** The study will remain blinded as to treatment allocation. The actual randomized treatment allocations will be kept by a contracted third-party responsible only for managing the randomization process. A variable indicating the blinded treatment allocations will not be part of the clinical study data to be managed by the data management clinical research organization (CRO). Therefore, only blinded study data will be available to the primary study statistician and responsible primary programming staff.<br>**Analysis Sets:**<br>• The intent-to-treat (ITT) analysis set will include all randomized patients.<br>• The As-Treated (AT) analysis set will include all randomized patients who were exposed to study medication (active or placebo). The AT analysis set will be used in the primary safety analyses with patients assigned to actual treatment received.<br>• The modified intent-to-treat (mITT) analysis will include all randomized patients who were exposed to study medication (active or placebo) and had a definitive diagnosis of abdominal sepsis or NSTI with patients assigned to their intended randomized assignment. The mITT set will be used in primary effectiveness comparisons.<br>• Supporting effectiveness analyses may be performed using a Per Protocol (PP) analysis set.<br>**Primary Analysis:** The primary efficacy comparison involves testing the following superiority hypotheses: **Ho:** $\pi_{0.50} - \pi_{Placebo} \leq 0$ **vs Ha:** $\pi_{0.50} - \pi_{Placebo} > 0$; where $\pi_{0.50}$ and $\pi_{Placebo}$ represent the true probability of freedom from durable loss of eGFR (alive, free of dialysis, and less than a 37% loss of eGFR (measured with the MDRD formula from the patient's reference eGFR)) at Day 28. Each probability represents the proportion of subjects on each arm expected to achieve freedom from durable loss of renal function. These hypotheses will be tested using an unadjusted chi-square test at a one-sided type 1 error rate of $\alpha$=0.025. The null hypothesis will only be rejected if the proportion of responders is larger in the active drug group compared to placebo.<br>**Sample Size Justification:** This trial will enroll 120 subjects that will be randomized in a ratio of 1:1 to either Reltecimod 0.50 mg/kg (n=60) or placebo (n=60), each in addition to SoC. Sample size analysis was performed assuming that all patients will be evaluable for the primary endpoint using last observation carried forward (LOCF) for patients missing a serum creatinine value on Day 28. |

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| | The primary efficacy hypothesis will be tested using an unadjusted $\chi^2$ statistic with a one-sided $\alpha$=0.025 significance level. The null hypothesis will only be rejected if the investigational drug demonstrates superiority. Statistical power was computed for a range of expected treatment group differences supported by the results of preliminary studies. Based on preliminary data, a total of 120 patients will be enrolled. This sample size results in 89% power if the true success rates are 75% and 50% for the investigational drug and placebo, respectively.<br><br>**Sample Size Re-Estimation:** A "Promising Zone" sample size re-estimation interim analysis is planned for when between 50% and 67% of the initial sample size is evaluable for the primary efficacy endpoint[53]). The purpose of the sample size re-estimation is to maintain (conditional) power when the treatment group difference is smaller than 0.25, but still clinically meaningful.<br><br>A pre-specified maximum sample size expansion will be specified prior to providing unblinded results to the independent data monitoring committee (iDMC) but in no case will the sample size expansion exceed an additional 200 subjects. With this restriction, only clinically meaningful treatment effects are detectable with good statistical power at the maximum sample size. The specific rules for determining if sample size expansion is permittable and if so, by how much, will ensure control of type 1 error.<br><br>Specifically, the sample size will be increased up to the maximum to maintain conditional power to as close to 80% as possible, but only if conditional power at the interim analysis is above a pre-specified threshold that results in control of type 1 error to the desired nominal value. If conditional power falls within the Promising Zone, increasing the sample size up to the pre-specified maximum is at the discretion of the Sponsor.<br><br>**Futility Analysis:** In addition to sample size re-estimation, a non-binding futility analysis will be conducted at the time of the interim analysis. If conditional power is below a pre-specified futility threshold, enrollment may be immediately stopped at the discretion of the Sponsor.<br><br>**Independent Data Monitoring Committee (iDMC):** A detailed iDMC charter will be provided to clarify all relevant issues relating to the conduct of the sample size re-estimation and futility analysis, including specific details regarding the operational procedures with fire-walls to protect against potential operational biases, decision rules, composition of the iDMC members and their conflict of interest statements.<br><br>**Adjudication Committee for Evaluation of AKI Stage and Recovery:** Experts chosen for the AKI Adjudication Committee will be independent of the Sponsor and neither they nor their institutions participated in the sample collection or sample measurement studies. Each adjudicator will be provided a form for each patient containing all relevant clinical information. Adjudicators will be blinded to group assignment and clinical data will be identified only by anonymized identification number. Adjudicators will indicate their assessment of AKI staging and recovery independently without consultation with each other. The basis for the adjudication will be the KDIGO consensus criteria corresponding to Stages 1-3 (mild to severe). A two thirds majority was predefined for use as the final adjudication.<br><br>**Secondary Endpoints:** Secondary endpoints have been specified from several domains including a similar endpoint but defined at Day 14. Additional secondary endpoints include time to the primary endpoint, AKI free days, SOFA over time, and critical care and hospital stay parameters (hospital length of stay (LOS), ICU and ICU-free days, ventilator days and –free days, vasopressor days and –free |

| | |
|---|---|
| | days). Analyses for these endpoints will generally be descriptive, with emphasis on characterizing clinical effect sizes. Nominal p-values will be presented. Categorical outcomes will be described using counts and percentages with nominal p-values determined through chi-square or exact methods. Critical care and hospital stay endpoints will be described using non-parametric approaches including using concordance statistics to characterize clinical effect sizes and Wilcoxon rank sum tests to determine nominal statistical significance. Methods appropriate for time-to-event endpoints including survival and life-table methods will be used for time-to-recovery endpoints.<br><br>**Safety Analysis:** The primary safety measures are Adverse Events (AEs) (including serious adverse events [SAEs]), clinical safety laboratory, physical exam, vital signs through Day 28 and determination of survival through Day 28. The safety profiles will be compared between active and placebo groups using descriptive statistics as appropriate for continuous and categorical safety variables. Changes in continuous safety measures such as laboratory values will be summarized by mean changes over time using descriptive statistics (mean, SD, median, minimum and maximum). The presence of clinically significant safety findings will be summarized by shift tables separately for each group using counts and percentages. AEs will be classified according to system organ class and preferred term and summarized by counts and percentages. AEs will also be summarized by relationship to study drug, severity, and whether they are serious. Specific summaries will involve AEs and SAEs in the Infection/Infestation system organ class. Results from physical exams will be tabulated for Screening, Day 7, and Day 14. For each test, the number of patients evaluated, and the numbers and percentages of patients with Normal and Abnormal results will be tabulated. Vital signs including weight, temperature, systolic blood pressure, diastolic blood pressure, respiration rate, and heart rate will be summarized across time (Screening, Day 1, Day 2, Day 3, Day 7, and Day 14 separately by treatment group by N, Mean, and SD. |

## 3. ABBREVIATIONS

| Abbreviation | Description |
|---|---|
| AE | Adverse Event |
| AKD | Acute kidney disease |
| AKI | Acute kidney injury |
| ALP | Alkaline phosphatase |
| ALT | Alanine transaminase |
| APC | Antigen-resenting Cell |
| ARDS | Acute respiratory distress syndrome |
| AST | Aspartate transaminase |
| AT | As-Treated |
| AUC | Area under the curve |
| CBC | Complete blood count |
| CFR | Code of Federal Regulations |
| CHF | Congestive heart failure |
| CI | Confidence Interval |
| CKD | Chronic kidney disease |
| CL | Clearance (plasma) |
| CLSI | Clinical and Laboratory Standards Institute |
| CNS | Central Nervous System |
| COPD | Chronic obstructive pulmonary disease |
| CPR | Cardiopulmonary resuscitation |
| CRO | Contract Research Organization |
| CRP | C-Reactive Protein |
| CRRT | Chronic renal replacement therapy |
| CT | Computed tomography |
| CVVH | Continuous Veno-Venous Hemofiltration |

| Abbreviation | Description |
|---|---|
| DLT | Dose limiting toxicities |
| DPO | Data Protection Officer |
| EC | Ethics Committee |
| ECC | Endogenous creatinine clearance |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EDC | Electronic data capture |
| eGFR | Estimated glomerular filtration rate |
| FDA | US Food and Drug Administration |
| $FiO_2$ | Fraction of Inspired Oxygen |
| GFR | Glomerular filtration rate |
| GCP | Good Clinical Practice |
| hCG | Human Chorionic Gonadotropin |
| hERG | Human Ether-a-go-go Related Gene |
| HIPAA | Health Insurance Portability and Accountability Act |
| IBW | Ideal Body Weight |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| ICU | Intensive Care Unit |
| iDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |
| IHD | Intermittent hemodialysis |
| IMP | Investigational Medicinal Product |

| Abbreviation | Description |
|---|---|
| IND | Investigational New Drug |
| IA | Interim analysis |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| IUD | Intra-uterine device |
| IV | Intravenous |
| KDIGO | Kidney Disease Improving Global Outcomes |
| KLH | Keyhole Limpet Hemocyanin |
| LAR | Legally acceptable representative |
| LOCF | Last observation carried forward |
| LOS | Length of stay |
| LPS | Lipopolysaccharide |
| MAR | Missing at random |
| MCAR | Missing completely at random |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHC | Major Histocompatibility Complex |
| mITT | modified Intent-to-Treat |
| MMRM | Mixed Model Repeated Measures |
| MTD | Maximum Tolerated Dose |
| NGAL | Neutrophil gelatinase-associated lipocalin |
| NOAEL | No Observed Adverse Event Level |
| NSAIDS | Non-steroidal anti-inflammatory drugs |
| NSTI | Necrotizing Soft Tissue Infection |
| NYHA | New York Heart Association |
| PAMP | Pathogen associated molecular patterns |

| Abbreviation | Description |
|---|---|
| $PaO_2$ | Partial pressure oxygen in arterial blood |
| PBMC | Peripheral Blood Mononuclear Cell |
| PE | Physical examination |
| PK | Pharmacokinetics |
| PP | Per Protocol |
| QTc | QT interval corrected |
| QTcF | QT interval corrected Fridericia |
| RRT | Renal replacement therapy |
| SAE | Serious Adverse Event |
| SA-AKI | Sepsis-Associated Acute Kidney Injury |
| SaO2 | Arterial oxygen saturation |
| SAP | Statistical analysis plan |
| SD | Standard Deviation |
| SoC | Standard of Care |
| SOFA | Sequential Organ Failure Assessment |
| SOP | Standard Operating Procedure |
| SpO2 | Peripheral capillary oxygen saturation |
| SSR | Sample size re-estimation |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TCR | T-cell Receptor |
| TEAE | Treatment Emergent Adverse Event |
| Th1 | T-Helper 1 Cell (CD4) subset |
| Th2 | T-Helper 2 Cell (CD4) subset |
| TNF | Tumor Necrosis Factor |
| US | Ultrasound |

| Abbreviation | Description |
|---|---|
| WBC | White Blood Cell |
| WFI | Water for Injection |
| WHO | World Health Organization |

# 4. INTRODUCTION

## 4.1 Background Information

### 4.1.1 Acute Kidney Injury

AKI is a common medical condition and results in hospital complications in critically ill patients. Its incidence among intensive care unit (ICU) patients has been reported to range between 16-67%[1], and in the US it occurs in approximately 20% of hospital admissions[2], and according to an Australian intensive care study, it is increasing every year by 2.8%[3]. AKI results in an abrupt decrease in kidney function and is associated with poor prognosis, extensive morbidity, increased short term and long term mortality and significant health care expenditures[4–78]. AKI is one of the most serious and common health complications, in the critical care setting (ICU), AKI is associated with a mortality rate of 60%[9], and despite advances in supportive care, mortality rates associated with AKI remain high. Depending on AKI severity, patients spend a long time in the ICU and hospital, may require long term dialysis treatment or kidney transplantation, may develop chronic kidney disease (CKD) or end stage kidney failure and represents an important burden in clinical practice.

Any stage of AKI has implications on both short term and long term outcomes[10]. As was reported by Lassnigg et al. 2004, even subtle increases in serum creatinine in surgical patients were found to be associated with an augmented mortality. Even patients with transient AKI experience worse long term outcomes[11].

A primary driver of AKI is sepsis, especially in critically ill patients, which account for 26% of cases in developed countries[1]. Clinical and basic science data indicate that sepsis-associated AKI (SA-AKI) is distinct from AKI without sepsis, based on characteristic pathophysiological mechanisms, unique profile of timing (onset and duration), and association with different short-term and long-term outcomes. Sepsis triggers a systemic cytokine-chemokine response, leading to end organ injury (which is manifested by cellular and subcellular injury: acute tubular necrosis, tubular and mesenchymal apoptosis, injury to the glomerulus, and inflammation of the nephron). Organ dysfunction secondary to sepsis is a significant contributor to mortality in critical care patients, regardless of the underlying septic cause. Furthermore, AKI can lead to inflammation and apoptosis in other organs besides the kidney, such as the lungs, heart and brain via organ cross talk[12].

With the lack of specific therapy for AKI that can either prevent AKI, hasten recovery of kidney function or abrogate the deleterious systemic effects of AKI, early detection of injury, coupled with initiation of appropriate supportive care and harm avoidance remain the mainstay of therapy.

Several components have been associated with development of AKI: inflammation, oxidative stress, apoptosis, and epithelial dysfunction. Among them inflammation has an important role, supported by evidence from both experimental models and clinical studies[13]. Following tissue injury at the site of sepsis, cells release damage associated molecular patterns (DAMPS), molecules that result in a further pro-inflammatory response

in distant organs, including the kidney through activation of immune cells (T cells and dendritic cells)[14].

### 4.1.2 Indication

The treatment indication is SA-AKI. The Investigational Medicinal Product (IMP) Reltecimod acts as an immunomodulator to attenuate CD28 activation of T-Helper 1 Cell 1 (CD4) subset (Th1) lymphocytes. Reltecimod is being developed for the treatment of SA-AKI in conjunction with standard of care (SoC), antibiotic therapy and supportive care.

The current study, ATB-203, is a Phase 3 clinical trial that will compare efficacy and safety of Reltecimod versus placebo (both in conjunction with SoC) for the treatment of SA-AKI.

### 4.1.3 Investigational Medicinal Product

Reltecimod (also known as AB103 or p2TA) is the acetate salt of the synthetic peptide that consists of 10 amino acids. Reltecimod has homology to amino acid residues 8-15 of the co-stimulatory receptor CD28 and has D-Ala residues abutted to N- and C-termini to render them more protease resistant. Binding of Reltecimod to CD28 is postulated to prevent activation of CD28 by B7 on the antigen-presenting cell (APC). Reltecimod has broad spectrum activity in animal models and was shown to inhibit pro-inflammatory cytokine induction without any evidence of agonist activity (up-regulation of cytokines) in response to bacterial toxins.

Reltecimod is a lyophilized powder, formulated to contain 1 mg/mL of the Reltecimod peptide, 30 mg/mL mannitol, and 3.6 mg/mL sodium chloride after reconstitution with sterile water for injection (WFI). The drug product to be used in clinical trials will be supplied in 20 mL vials. Each vial contains nominal amounts of the API and excipients as follows: 10.5 mg of Reltecimod, 315 mg of mannitol, and 37.8 mg of sodium chloride.

Prior to use, each vial of drug (10.5 mg) is solubilized in 10.5 mL of WFI to generate a drug concentration of 1 mg/mL. 10 mL (10 mg Reltecimod) will be withdrawn from each vial and pooled together with 10 mL from additional vials, to constitute the final amount (volume) of drug needed for each patient (based on individual patient's actual body weight).

The reconstituted drug product is administered directly and is not diluted prior to administration. It will be administered at a dose of 0.50 mg/kg as an intravenous infusion given over 10 minutes.

Encouraging results from non-clinical (See Section 4.1.3.2) and clinical studies (Phase 1 and 2; see Section 4.1.3.3) indicate a good safety profile with no reported toxicities in animals or humans as well as potential efficacy in this patient population.

#### 4.1.3.1 Mechanism of Action

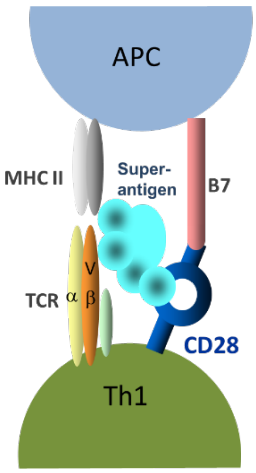
CD28 is a co-stimulatory receptor, which is a critical regulator of the immune response. Expressed constitutively on naïve T cells (mostly CD4+ and CD8+), CD28 is a homodimer. Its signal is mediated by dimerization and binding to its ligands on the APC, delivering a strong activation signal to the effector cell. This signal is required to avoid an apoptotic or anergic response by the lymphocyte. CD28 interacts with its B7 co-ligands (B7.1 (CD80)

and B7.2 (CD86), residing on APCs). This interaction transduces the signal that is essential for an immediate T-cell response and regulates early antigen signaling. A major component of such interaction is the induction of an inflammatory response, mediated by multiple pro-inflammatory cytokine and chemokine production and release. There is growing appreciation that T-cell and APC interactions play a critical role in inflammatory response of severe infections and link the adaptive and innate immune systems. Inflammation is a protective response that is intended to eliminate the initial cause of cell injury, as well as any necrotic cells and tissues resulting from the original insult, and to initiate the process of repair. Acute or chronic inflammation might lead to a multitude of diseases and is therefore normally closely regulated. Amplified and dysregulated inflammatory response is triggered by various insults causing cellular injury (pathogen- and non-pathogen induced), eliciting exaggerated response and overexpression of pro-inflammatory cytokines and chemokines (cytokine storm), that are harmful to the host.

Major inducers of the inflammatory response include bacterial exotoxins and endotoxins, as well as external stimuli. During Gram-positive bacterial infection exotoxins such as superantigens, stable proteins that stimulate virtually all T cells, without a need for processing by APC are secreted[15–17]. Bypassing the restricted presentation of conventional antigens, superantigens can activate 30-50% of T cells to divide and produce cytokines. In contrast to conventional immune response, during which 0.01% of T cells react with antigens to orchestrate immune attack without harming healthy tissue, superantigens activate the cellular immune response at least 5,000-fold more strongly than do ordinary antigens. Toxic shock results from a sudden and massive induction of Th1 cytokines including interleukin-2 (IL-2), interferon gamma (IFN-γ), and tumor necrosis factors (TNF)[18–20].

Induction of these Th1 cytokines can occur through the binding of a superantigen (produced by Gram-positive bacteria) to the major histocompatibility class II (MHC II) complex (located on the surface of an APC), and the T-cell receptor (TCR, located on the surface of a Th1 cell). However, this interaction is insufficient for activation. Superantigens must also bind to CD28. By engaging all 3 receptors simultaneously, the superantigen overcomes its inherently limited affinity for each, allowing it to deliver a strong activation signal (Figure 1).

**Figure 1: Th1 induction**




Binding sites of superantigen (blue) in the immunological synapse. Direct binding of superantigen to CD28 is triggering activation of CD28

In addition to this superantigen-mediated mechanism, the inflammatory response can be triggered by endotoxin-producing bacteria (e.g. Gram-negative bacteria or mixed infections). The prototypical example of a bacterial endotoxin is lipopolysaccharide (LPS), found in the outer membrane of various Gram-negative bacteria. LPS toxicity (in addition to TLR4 signaling) involves the co-stimulatory molecule CD28 and its B7 ligand, which upregulates the co-receptors for CD28 co-activating signals, CD80/86, and thereby amplifies CD28-CD80/86 signaling[21,22]. In addition, CD28 is an important mediator in LPS-induced septic shock[23], and in cases of Gram-negative infections[24] or polymicrobial infections[25,26].

***Inflammatory response in AKI***: AKI is a major complication of sepsis, and SA-AKI is regarded as the foremost precipitant of AKI. Sepsis-associated AKI portends a high burden of morbidity and mortality in patients with critical illness, and represents a distinct subset of AKI, contributing to a unique constellation of hemodynamic, inflammatory and immune mechanisms[1].

The precise mechanisms that lead to AKI during sepsis remain unknown. It is recognized that the pathogenesis of SA-AKI is a multifactorial process involving an interplay between inflammation, apoptosis and oxidative stress. Novel therapies directed at these pathways are now being considered as potential therapies.

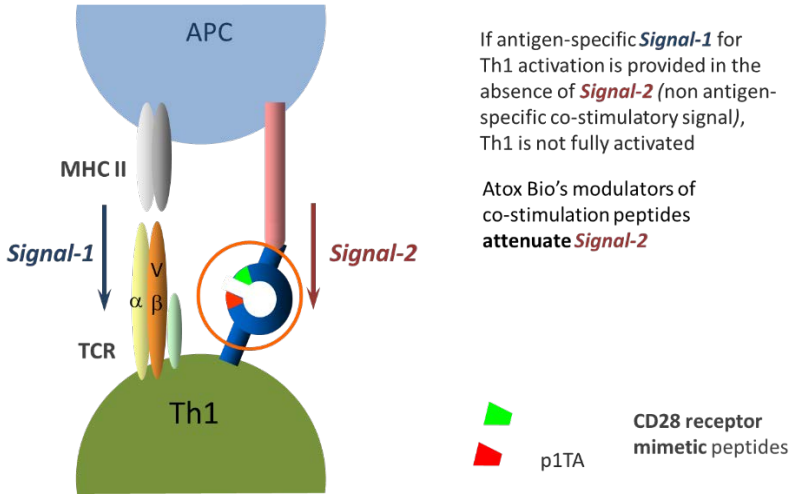
It has been accepted that the inflammatory component, especially innate immunity, has an important contribution to the development of renal injury, and therefore, the immune pathway has been acknowledged as a target for developing therapies for AKI. The inflammatory response involves the inflammasome which integrates danger signals into caspase activation and secretion of pro-inflammatory cytokines[27]. Depletion of T cells to very low levels leads to protection against renal injury[28]. In particular the co-stimulatory pathway of T cells activation via CD28 and CTLA4 has been shown to have a substantial role in experimental SA-AKI[29]. In several models, it has been demonstrated that blocking the co-stimulation can be beneficial and protects the kidney: Using CD28 knock-out mice,

animals were protected from LPS-induced acute renal failure[24]. CTLA4-Ig (a competitive inhibitor of CD28-B7 interaction) protected mice from renal injury[30]. Our own data indicated that in a model of SA-AKI, Reltecimod conferred improved outcome (both survival benefit and renal function). In accordance, therapies modulating the immune response (such as alkaline phosphatase), were shown to improve outcome in experimental and clinical SA-AKI[31].

In view of the significant role of CD28 in triggering inflammatory response, it was defined as a therapeutic target.

***Reltecimod effect***: Reltecimod is the sodium salt of a synthetic peptide that consists of 10 amino acids and has homology to amino acid residues 8-15 of the T-lymphocyte molecule CD28, residues that are part of its homodimer interface. Reltecimod is postulated to bind to the opposing monomer of CD28 and as such, to prevent activation of CD28 by B7 on the APC and modulate the interaction between host T cells (host factors) and pathogen associated molecular patterns (PAMPs) such as superantigens and endotoxins. As a result, Reltecimod attenuates the excessive inflammatory response mediated by co-stimulation (Figure 2) by modulating CD28 signaling, but not blocking it completely, thus maintaining the normal immune response.

**Figure 2: Reltecimod function**




*CD28 signaling can be blocked by peptide mimetics of the contact region in each ligand: the two rims (red and green) of the dimer interface predicted for CD28.*

Reltecimod was originally designed and developed towards creating a broad-spectrum countermeasure directed against the superantigen toxin family, for the treatment of Gram-positive bacterial superantigen toxicity. Reltecimod prevents the binding of superantigens to CD28 and subsequent activation of the downstream cellular cascade. As superantigens play a critical role in the pathogenesis caused by Gram-positive bacteria, Reltecimod could modulate the interaction between the host and pathogen factors, inhibiting their harmful effects and providing a clinical benefit. Nevertheless, binding of Reltecimod to CD28 was found to also intervene with the downstream signaling of CD28 independently of superantigens: as Reltecimod binds directly to CD28 on the opposing monomer, it can therefore intervene with the downstream signaling of CD28 in cases that are not mediated

by superantigens. As such, Reltecimod was found to be a potent attenuator of lethal inflammatory signaling induced by multiple pathogens, including Gram-positive and Gram-negative bacteria as well as viral pathogens. The role of the co-stimulatory pathway in the interaction of bacterial endotoxins with host cells has not been fully characterized, however, evidence exists that it has a role in LPS-mediated effects in endotoxin-induced Gram-negative infections[32–35]. Further support for the role of the co-stimulatory pathway in Gram-negative infection in animals and in sepsis patients was demonstrated using CD28 knock out mice[25,26].

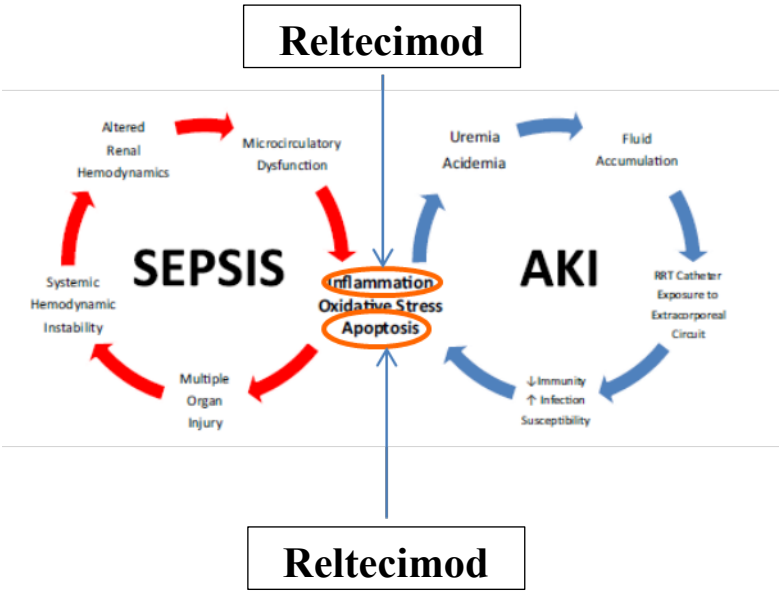
The mechanism of Reltecimod is unique as it does not involve down-regulation of the normal humoral immune response, is not affecting anti-inflammatory T-Helper 2 Cell (CD4) subset (Th2) response and does not block the protective B cell immune response[36].

Further, Reltecimod does not function as a CD28 agonist as it does not stimulate cytokine production *in vitro*, nor have detrimental effects on intoxicated (superantigen-treated) animals or animals infected with live bacteria. In addition, Reltecimod does not induce intracellular cytokine production ex vivo (tested in a large set of T-cell subsets that were isolated from healthy volunteers in a Phase 1 study following Reltecimod administration).

Thus, Reltecimod is both a superantigen and a CD28 antagonist (acting to modulate their biological activity), its activity is not pathogen specific, and it is a host-oriented, broad spectrum attenuator of cytokine storm. Reltecimod can therefore be employed to treat infections from various sources having a substantial inflammatory component, such as SA-AKI. Indeed, Reltecimod has been shown to have broad spectrum activity in animal models and inhibit pro-inflammatory cytokine induction in several conditions involving inflammatory response without any evidence of agonist activity (up-regulation of cytokines) in response to bacterial toxins.

As Reltecimod has been shown to modulate the inflammatory response via attenuation of the CD28 co-stimulatory pathway[36,37] and to be associated with decrease in apoptosis in kidney, it is postulated to have protective therapeutic effect in patients suffering from SA-AKI by intervening with key important processes (inflammation and apoptosis) that contributes to both sepsis and AKI development (Figure 3).

**Figure 3: Potential role for Reltecimod in AKI**




*Adjusted from Alobaidi et al., 2015. Reltecimod can modulate with pathophysiological processes that contributes to both sepsis and AKI*

#### 4.1.3.2 Non-clinical Safety Studies

The non-clinical toxicology and safety pharmacology of Reltecimod has been tested *in vitro* and in in a single-dose toxicology study in mice, repeat-dose toxicology studies in mice, pigs and minipigs, and fertility and embryo-fetal developmental studies in mice, and embryo-fetal developmental study in rabbits. the central nervous system (CNS) safety pharmacology study was performed in mice, and cardiovascular safety study performed in pigs and minipigs. Data from these studies are summarized below.

***In Vitro* Toxicology Studies**

- Reltecimod was not toxic to human or pig peripheral blood mononuclear cells (PBMCs) *in vitro* at concentrations from 0.01 to 10 µg/mL (study GCF0007).
- Reltecimod at concentrations of 4, 20 and 100 µg/mL, mixed with human blood at a volume ratio of 0.4 (2:5) test material:blood, did not cause hemolysis. In the human, this ratio corresponds to an administration of 3.2 mL/min intravenous infusion rate (study GCF0009).
- Reltecimod, when mixed with human plasma at concentrations of 4, 20, and 100 µg/mL at a ratio of 0.4 (2:5) test material:plasma, showed no adverse reactions such as flocculation, precipitation, or coagulation (study GCF0009).

***In Vivo* Toxicology Studies**

- In an acute maximum tolerated dose (MTD) toxicology study in male and female mice (Study GCF0012), Reltecimod given IV at 2, 4, 8, or 16 mg/kg was well tolerated with no toxicologically important clinical signs, no dose-related

effects on body weight or food consumption during the observation period and no abnormalities observed at macroscopic examination. Based on the general good clinical condition of the animals and the absence of any clear indicators of toxicity, the MTD for Reltecimod was not determined within the context of this study.

- In a pharmacokinetic (PK) study in male mice (Study MPS00022) with single dose Reltecimod (5 mg/kg), no clinically relevant abnormalities were noted throughout dosing and sample collection.
- In a repeat dose toxicology GLP study in male and female CD-1 mice (Study MPS0025), Reltecimod was administered IV for 14 consecutive days at doses of 0.3, 1.25, and 5 mg/kg/day. There were no Reltecimod-related changes seen in clinical observations, body weights, food consumption, or serum chemistry parameters. A non-adverse increase in absolute white blood cells (2.0 × control) and absolute neutrophil count (3.0 × control) was noted in male animals dosed at 5 mg/kg/day on Day 15, but all recovered after a 2-week recovery period. The no-observable-adverse-effect-level (NOAEL) for this study was considered to be greater than 5 mg/kg/day.
- In a repeat dose toxicology GLP study in male and female Yorkshire pigs (Study MPS00012), Reltecimod was administered to 7 to 15 kg pigs by slow bolus IV injection (10 mL/kg volume) once daily for 14 consecutive days at doses of 0.6, 2.5, and 5.0 mg/kg/day. In the main study, pigs were sacrificed the day after dosing and another group after a 14-day recovery period. No toxicologically-relevant effects were seen in this study. It was concluded that the apparent NOAEL is greater than 5.0 mg/kg.
- In a repeat dose toxicology GLP study in male and female Gottingen minipigs (Study 20156690), Reltecimod Sodium was administered once weekly by intravenous 10-min infusion for a minimum of 14 days (i.e., dosing on Days 1, 7, and 14) at doses of 5, 15 and 50 mg/kg/dose. There were no early deaths, test article-related clinical signs, gross necropsy findings, or microscopic pathology findings. There were no changes in body weights, body weight gains, food consumption, respiratory assessments, ophthalmology, electrocardiography, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), or organ weights. Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 50 mg/kg/dose, the highest dose tested. This corresponded to males and females mean Cmax = 90,100 ng/mL (males), 141,000 ng/mL (females) and mean AUC(0-t) = 783,000 ng*min/mL (males), 1,100,000 ng*min/mL (females) on Day 14. The exposures of Reltecimod in this study were at least 100-fold above the exposure in healthy human volunteers, and at least 50-fold above the exposure in NSTI patient.
- In a fertility toxicology GLP study in male CD-1 mice (study 01136002), Reltecimod sodium was administered via intravenous injection (bolus) via

vascular access buttons (VAB) once daily for 28 days prior to mating and continuing through 1 day prior to euthanasia for a total of 56 to 57 doses at dose levels of 5, 15, and 50 mg/kg/day. There were no test article-related effects on survival. One male in the 15 mg/kg/day group was found dead on Study Day 51 in the absence of clinical observations, effects on body weight or food consumption, and gross necropsy observations. In the absence of mortality noted at the highest dosage level of 50 mg/kg/day, this death was not considered test article-related. One male in the control group was sent to necropsy in extremis on Study Day 48. All other males survived to the scheduled necropsy. There were no test article-related clinical observations at the daily examinations or 5–15 minutes following dose administration at all dosage levels. Mean absolute body weights, body weight gains, and food consumption for males in the 5, 15, and 50 mg/kg/day groups were unaffected by test article administration throughout the treatment period (pre- and post-mating period). There were no test article-related effects on male reproductive performance (mating, fertility, and copulation indices), spermatogenic parameters (motility, concentration, sperm production rate, and morphology), or pre-coital intervals at any dosage level. There were no test article-related macroscopic findings or effects on organ weights in the 5, 15, and 50 mg/kg/day group males. The mean numbers of implantation sites and intrauterine survival of the embryos were unaffected by test article administration to the males at 5, 15, and 50 mg/kg/day. In conclusion, there were no effects on survival, clinical observations, body weights, body weight gains, food consumption, reproductive endpoints, gross necropsy findings, organ weights, or intrauterine survival. Therefore, a dosage level of 50 mg/kg/day, the highest dosage level tested, was considered to be the no-observed-adverse-effect level (NOAEL) for male systemic and reproductive toxicity and early embryonic toxicity of Reltecimod sodium administered by intravenous injection (bolus) to Crl:CD1(ICR) mice.

- In a fertility and embryonic developmental toxicity GLP study in female CD-1 mice (study 01136006), Reltecimod sodium was administered via intravenous injection (bolus) via vascular access buttons (VAB) once daily for 14 days prior to mating and continuing through Gestation Day 7 for a total of 24-30 doses at dose levels of 5, 15, and 50 mg/kg/day. There were no test article-related effects on survival. One female each in the control, 5, 15, and 50 mg/kg/day groups were found dead or euthanized in extremis during the study. In the absence of other signs of toxicity at any dosage level, the single deaths or moribundity noted in the test article-treated groups were not considered test article-related. All other females survived to the scheduled necropsy. There were no test article-related clinical observations at the daily examinations or 5–15 minutes following dose administration at all dosage levels. Mean absolute body weights, body weight gains, and food consumption for females in the 5, 15, and 50 mg/kg/day groups were unaffected by test article administration throughout the treatment period. There were no test article-related effects on female

reproductive performance (female mating, fertility, and conception indices, estrous cyclicity, and numbers of days between pairing and mating). There were no test article-related macroscopic findings or effects on organ weights in the 5, 15, and 50 mg/kg/day group females. The mean numbers of corpora lutea and implantation sites and intrauterine survival of the embryos were unaffected by test article administration at 5, 15, and 50 mg/kg/day. In conclusion, the dosage level of 50 mg/kg/day, the highest dosage level tested, was considered to be the no-observed-adverse-effect level (NOAEL) for female systemic and reproductive toxicity and early embryonic toxicity of Reltecimod sodium administered by intravenous injection (bolus) to female Crl:CD1(ICR) mice.

- In an embryo-fetal developmental toxicity GLP study in female CD-1 mice (Study 01136003), Reltecimod sodium was administered via tail intravenous injection (bolus) once daily during Gestation Days 6–15 at dose levels of 5, 15, and 50 mg/kg/day. All animals survived to the scheduled necropsy on Gestation Day 18, including 1, 2, and 1 females in the control, 5, and 15 mg/kg/day groups, respectively, that delivered on the day of scheduled necropsy (Gestation Day 18). No test article-related clinical observations were noted at the daily examinations or 5–15 minutes following dose administration at any dosage level. Mean maternal body weights, body weight gains, net body weights, net body weight gains, gravid uterine weights, and food consumption were unaffected by test article administration. There were no test article-related macroscopic findings noted at any dosage level at the scheduled necropsy on Gestation Day 18. Intrauterine growth and survival were unaffected by test article administration at all dosage levels. There were no test article-related fetal malformations or developmental variations observed in all groups. Based on the absence of any maternal or embryo/fetal developmental effects at any dosage level, a dosage level of 50 mg/kg/day, the highest dosage level evaluated, was considered to be the no-observed-adverse-effect level (NOAEL) for maternal toxicity and embryo/fetal development when Reltecimod sodium was administered via intravenous injection (bolus) to Crl:CD1(ICR) mice. This corresponded to a mean Cmax value of 289,000 ng/mL and a mean $AUC_{0\text{-}20min}$ value of 950,000 (ng·min/mL) on Gestation Day 15. The exposures of Reltecimod in this study were at least 100-fold above the exposure in healthy human volunteers, and at least 50-fold above the exposure in NSTI patient.
- In an embryo-fetal developmental toxicity GLP study in female NZW rabbits (Study G17034), Reltecimod sodium was administered via 1-min intravenous infusion once daily from implantation on Gestation Day (GD) 6 to closure of the hard palate on GD 18 at dose levels of 5, 15, and 50 mg/kg/day. There were no mortalities and no adverse clinical signs in any of the treated females at any of the doses tested. The mean body weight, body weight gain and food consumption of rabbits at all test item-treated groups were statistically comparable to the vehicle control group. There were no test item-related macroscopic findings at any dosage level at the scheduled necropsy on GD 29.

Maternal parameters comprising of uterine weight, number of corpora lutea, implantations and early and late resorptions in the test-item-treatment groups were comparable to the vehicle control. Gross evaluation of placenta revealed no findings. The litter parameters comprising of total number of fetuses, number of live fetuses, male and female fetal weights were comparable to the vehicle control group at all tested doses. No abnormality related to the test item was noticed at the external, visceral and skeletal examination of fetuses at any of the doses tested. Based on the absence of adverse findings under the conditions and doses employed in this study, it is concluded that No Observed Adverse Effect Level (NOAEL) for maternal and fetal developmental toxicity is 50 mg/kg/day, the highest dose tested. This corresponded to a mean Cmax value of 387,000 ng/mL and a mean AUClast value of 1,130,000 (ng·min/mL) on Gestation Day 18. The exposures of Reltecimod in this study were at least 100-fold above the exposure in healthy human volunteers, and at least 50-fold above the exposure in NSTI patient.

- In an immunotoxicology study in male and female mice (Study 302111), Reltecimod was administered by a slow bolus IV injection on Days 1, 8, 15, and 22. On Day 15, the potent T-cell immunogen, keyhole limpet hemocyanin (KLH), (0.5 mL of 0.2 mg/mL in sterile water; 100 µg) was administered by intraperitoneal injection. Mice were observed for clinical signs and death. Blood immunophenotyping was conducted at scheduled necropsies as well as primary immunoglobulin M (IgM) and immunoglobulin g (IgG) antibody responses to KLH. Reltecimod given weekly for 4 weeks at doses of 1.25, and 5 mg/kg/dose were well tolerated. Although there were some variations in the immunotoxicity assessments, these were deemed not to be significant Reltecimod-related changes (blood immunophenotyping) or related to the administration with peptide. Statistically significant decreases in thymic weights in males given ≥1.25 mg/kg/dose of peptide Reltecimod may have been related to test article administration; however, these had no histologic correlate and were reversible. In addition, higher thymus weights in females, as compared to males, are regarded as a normal phenomenon for mice, which was also consistent with the historical data and published observations. The NOAEL in this study was considered to be 5 mg/kg due the reduction in thymus weights in male mice.

**Safety Pharmacology Studies**

- Reltecimod at a concentration of 10 µg/mL had no significant effect on human ether-à-go-go related gene (hERG) tail current, in human embryonic kidney cells (HEK-293) stably transfected with hERG ion channel cDNA. This is a measurement of potential QT interval corrected (QTc) prolongation (GLP study GCF0014).
- In the repeat dose toxicology GLP study in Yorkshire pigs (Study MPS00025) described above, Reltecimod at up to 5.0 mg/kg did not cause toxicologic effects

on electrocardiogram (ECG) interval durations. In particular, there was no effect of treatment on QT or QTc intervals.

- In the repeat dose toxicology GLP study in male and female Gottingen minipigs (Study 20156690) described above, relevant safety pharmacology measures were incorporated into the study and included respiration rate and electrocardiographic parameters. Reltecimod was administered intravenously with syringe pumps over 10-minutes once weekly for a minimum of 14 days (i.e., dosing on Days 1, 7, and 14) at dosages of 0 (phosphate buffered saline), 5, 15, and 50 mg/kg. For respiratory assessment, animals were monitored for respiratory rates on Day 7 at approximately 120 minutes post start of infusion. Respiratory rates were visually examined at 6-second intervals and multiplied to average breaths taken per minute prior to electrocardiogram (ECG) collection. ECG measurements were obtained from all animals using leads I, II, III, aVR, aVL, and aVF. The ECG measurements were obtained once pretreatment (Day -7), on Day 7 at approximately 120 minutes post start of infusion, and during the last week of the recovery period (Day 25). Only lead II was evaluated by a board-certified veterinary cardiologist. Tracings were evaluated for the ECGs performed pretreatment and on Day 7. Quantitative ECG parameters measured included HR, RR interval, PR interval, QRS duration, QT and QTc (Fridericia's) interval. Reltecimod did not alter respiration rates or ECG rhythm, morphology, or quantitative ECG measurements in male or female minipigs examined on Days -7, 7 and 25. Reltecimod had no physiologically relevant effects on respiratory rate or electrocardiographic parameters in minipigs at doses up to 50 mg/kg.
- In a mouse CNS safety pharmacology GLP study (Study MPS00023), Reltecimod was administered once by bolus IV injection on Day 1 of the study at doses of 0, 0.3, 1.25, and 5 mg/kg. A CNS screen was performed 2 minutes and 24 hours after dosing. There were no biologically important differences among the dose groups for the male and female mice in the measures of behavior, autonomic functions, appearance, grip strength or body temperature during the 2 minute or 24 hour post dosing CNS screen. Based on these data, the NOAEL of Reltecimod for neurobehavioral measures of the CNS screen in mice is greater than 5 mg/kg (the highest dose tested).

**Non-Clinical Pharmacology Studies**

Reltecimod has been shown in animal models to:

1. Protect mice from SEB-induced lethal shock.
2. Protect mice from LPS-induced lethal shock.
3. Protect mice (improve survival and inflammatory response) from lethal Gram-positive and Gram-negative bacterial infections (*S. pyogenes, S. pneumonia, E. Coli,* Polymicrobial infections [CLP]).

4. Improve survival and functional renal outcome of mice in a model of sepsis-induced AKI.

Thus, Reltecimod shows activity in both Gram-positive and Gram-negative models of sepsis and septic shock. For an extensive description of the non-clinical pharmacology studies, refer to the Investigator's Brochures.

#### 4.1.3.3 Clinical Studies

Reltecimod has been evaluated in two safety and pharmacokinetic (PK) clinical studies, a Phase 1 study in healthy volunteers (study no. ATB-001) and a Phase 2 study in NSTI patients (study no. ATB-201).

##### 4.1.3.3.1 Phase 1 Study ATB-001

The Phase 1 single center, randomized, double-blind, placebo-controlled, sequential-dose escalation study was conducted in 25 healthy volunteers. Four different escalating dose levels of Reltecimod were evaluated: 7.5 μg/kg, 37.5 μg/kg, 150 μg/kg and 450 μg/kg with a placebo control (1 or 2 subjects) included in each cohort; each subject received a single intravenous infusion of Reltecimod or placebo (saline) control. Blood was collected for PK and flow cytometry assessments of leukocyte subsets after infusions. Subjects were assessed 1-day and 6- to 8-days after the infusions for adverse events (AEs), vital signs, and clinical laboratory parameters. The primary objective of this study was to establish the safety profile and MTD of Reltecimod given as a single intravenous infusion in healthy volunteers. The secondary objective was to determine the PK profile of Reltecimod in humans after a single intravenous infusion. In addition, lymphocyte profiling was performed on subjects from the high dose cohort 4. PBMCs were obtained and subjected to flow cytometric analysis, for phenotypic analysis and intracellular cytokine expression. Study duration was 14 days.

A total of 22 AEs were reported during the conduct of the trial, of which 21 (95.5%) were mild and only one was moderate in severity. Of all the subjects in the study, seven had AEs and 18 had no AEs. None of the AEs were considered related to Investigational Product. There were no dose-limiting toxicities nor were there any serious adverse events (SAEs). There were no clinically meaningful changes in vital signs, clinical laboratory parameters, ECG parameters or lymphocyte subsets.

Lymphocyte profiling: Although variability between subjects was apparent, for the most part within a subject over time, the percentages of positive cells and absolute counts remained similar to those at baseline.

**PK in healthy subjects:** Pharmacokinetic parameter estimates are shown below:

**Table 1: Summary of Reltecimod pharmacokinetic parameters in healthy volunteers**

| Dose µg/kg | $C_{max}$ ± SD ng/mL | $AUC_{0-t}$ ± SD ng-min/mL | $T_{1/2}$ ± SD Min | CL ± SD mL/min/kg |
|---|---|---|---|---|
| 7.5 | 10.14 ± 2.22 | 61 ± 19 | ND | ND |
| 37.5 | 56.67 ± 30.28 | 523 ± 248 | 1.36 ± 0.51 | 85 ± 50 |
| 150 | 208.80 ± 51.37 | 2,137 ± 370 | 1.26 ± 0.28 | 72 ± 11 |
| 450 | 707.74 ± 269.03 | 6,082 ± 2022 | 1.34 ± 0.21 | 80 ± 22 |

$AUC_{0-t}$ =area under the curve from time zero to the last measurable time point, CL=clearance, $C_{max}$= maximum concentration, ND = not determined, insufficient data to calculate, SD=standard deviation, $T_{1/2}$ =half-life.

Plasma Reltecimod concentrations in all cohorts peaked near the end of the infusion and declined rapidly with a $T_{1/2}$ of a little over one minute. The apparent elimination $T_{1/2}$ was very similar across dose levels. Systemic exposure to Reltecimod as measured by $C_{max}$ and area under the curve (AUC) appeared to be dose-proportional. Consequently, plasma clearance (CL), which was derived from AUC and dose, was similar for all doses. The apparent volume of distribution, approximately 200 mL/kg, is much larger than plasma volume, which is consistent with distribution to sites outside the plasma compartment.

**Summary:** Overall, Reltecimod given IV at doses up to 450 µg/kg was very well tolerated in healthy volunteers. Following a 10-minute intravenous infusion of Reltecimod to healthy volunteers, plasma concentrations peaked at the end of infusion and then declined rapidly with an apparent elimination half-life of a little over one minute. Exposure was dose-proportional.

#### 4.1.3.3.2 Phase 2 study ATB-201

The Phase 2 study (ATB-201) was a multicenter, randomized, double blind, first-in-patients exploratory study in subjects who had a clinical diagnosis of necrotizing soft tissue infection (NSTI) and scheduled to undergo urgent surgical exploration and debridement. The study was conducted in seven clinical sites in the US and included 40 patients evaluated for efficacy. Patients were randomized to receive either Reltecimod as a single intravenous infusion of 0.50 mg/kg or 0.25 mg/kg, or placebo (saline), over 10 minutes. Study drug or placebo was administered within 6 hours from clinical diagnosis, in addition to SoC (including prompt and repeated aggressive surgical debridement, aggressive resuscitation and physiologic support, and antimicrobial drugs).

The study objectives were to determine safety and PK of Reltecimod and the potential treatment benefit compared to placebo, by clinical benefit (measured by resolution of systemic inflammatory parameters, resolution of organ dysfunction or failure, and the need for repeated surgeries for the primary infection), assess critical care/ pharmacoeconomic benefit by hospital length of stay, ICU length of stay/ICU-free days, vasopressors free days, and mechanical ventilation days/ free days, and define potential surrogate biomarkers. Study duration was 28 days. A post-hoc analysis was performed to determine the incidence

of AKI in this population of patients with NSTI and to evaluate the effect of Reltecimod in improving the recovery from AKI as compared to placebo.

***Safety results***: Safety was evaluated in the ITT population, comprised of all study participants who were randomized and received study drug or placebo (n=43; includes 3 patients who were dosed but not evaluated for efficacy due to not meeting inclusion/exclusion criteria). Due to the natural severity of the underlying disease, a high incidence of AEs was expected in the study population. Patients in the High dose group presented with a more severe state of the disease, as exemplified by a higher rate of AEs, SAEs, and abnormal labs on Day 0 (before study drug administration). Post Day 0 (after drug administration) and over the course of the study, AEs were reported in 94.1%, 93.3% and 81.8% of patients in the High dose, Low dose and placebo groups, respectively, with no statistically significant difference. No study drug-related AEs were reported. Most of the AEs were mild or moderate. Severe AEs were reported in two patients (11.8%) of the High dose group, two patients (13%) of the Low dose group and three patients (27.3%) of the placebo group.

Five patients (29.4%), 8 patients (53.3%), and four patients (36.4%) in the high dose, Low dose, and placebo groups, respectively experienced an SAE after Day 0. All SAEs (except one SAE of acute renal failure in a patient of the placebo group that had a background condition of chronic renal disease) were assessed as related to the underlying disease of NSTI, and none was regarded as study drug-related.

Four patients died during the study; one patient in each of the high and low dose groups and two patients in the placebo group. In both patients of the Reltecimod-treated groups, the cause of death was multi-organ failure related to the underlying disease of NSTI, and in the placebo group one patient died of respiratory failure and cardiac arrest, and the second patient died of septic shock that started already at Day 0 and multi-organ failure related to NSTI.

In addition, there were no significant trends or findings related to laboratory abnormalities that could be attributed to study drug administration.

An ECG was performed on Day 0 prior to study drug administration and within 6 hours post study drug administration on Day 1. Comparator groups demonstrated similar means and distribution of QT interval corrected Fridericia (QTcF) values. Treatment groups did not have higher mean change in QTc than placebo and outliers were similar in number and scale.

Overall, intravenous infusion of Reltecimod at doses of 0.50 mg/kg and 0.25 mg/kg over a 10-minute infusion period was well tolerated in this patient population and no significant safety signals or trends were observed.

***PK results:*** Following a 10-minute intravenous infusion of Reltecimod to NSTI patients before, during, or after surgery, plasma drug concentrations peaked at the end of infusion. Plasma Reltecimod concentrations declined with a half-life of approximately 5 minutes in the high and low dose groups. Systemic Reltecimod exposure, as measured by $C_{max}$ and AUC, appeared to be dose-proportional when comparing these parameters across the two dose groups (Table 2). There were no obvious differences in plasma Reltecimod

concentrations between samples collected from venous lines compared to those collected from arterial lines. There also did not appear to be a clear effect of dosing time relative to surgery. Plasma Reltecimod concentrations in patients treated before, during, or after surgery did not show any apparent differences.

**Table 2: Reltecimod pharmacokinetic parameters in NSTI patients**

| **PK Parameters** | | | | | | |
|---|---|---|---|---|---|---|
| **Treatment group** | **Statistic** | **$C_{max}$ ng/mL** | **$T_{max}$ min** | **$AUC_{0-\infty}$ ng-min/mL** | **$T_{1/2}$ min** | **CL mL/min/kg** |
| 0.50 mg/kg | Mean | 1,503 | 10.60 | 16,020 | 5.75 | 39.89 |
| | SD | 655 | 4.82 | 7,086 | 3.64 | 24.46 |
| | Median | 1,352 | 10.00 | 16,921 | 4.89 | 29.55 |
| | | | | | | |
| 0.25 mg/kg | Mean | 961 | 6.73 | 7,733 | 4.80 | 43.17 |
| | SD | 681 | 2.80 | 4,021 | 6.30 | 26.68 |
| | Median | 899 | 5.00 | 8,497 | 2.61 | 29.42 |

The PK studies in human confirm the short elimination half-life of the product, and that the systemic clearance (CLs) values demonstrate that the clearance processes involved are of high capacity and rate.

#### 4.1.3.3.3 Post-hoc analysis in SA-AKI patients (Study ATX1002K)

The clinical efficacy of Reltecimod in SA-AKI was for the first time evaluated in a post-hoc analysis (Study ATX1002K), using the subset of NSTI patients from Study ATB-201 who developed AKI as part of their disease process. AKI patients were defined as patients having at least one creatinine value (from baseline through Study Day 7), which was at least 1.5 times higher than the pre-illness reference value.

The primary objective of this post-hoc analysis was to identify the subset of patients with NSTI that also suffered from AKI, and to assess the clinical benefit of Reltecimod on AKI in this specific population of NSTI patients with AKI. Clinical measures for assessment of efficacy were serum creatinine (also used for calculating recovery rate from AKI) and neutrophil gelatinase-associated lipocalin (NGAL) in plasma.

Patients were staged according to the Kidney Disease Improving Global Outcomes (KDIGO guidelines, 2012) criteria[38]. Based on KDIGO staging, 18 patients (45%) were identified as having AKI, as part of their disease condition. The incidence of AKI among the 3 treatment groups was similar, with 7 patients (47%) each in the 0.50 mg/kg and 0.25 mg/kg Reltecimod groups, and 4 patients (40%) in the placebo group, respectively. The overall AKI rate in this study was found to be similar to literature data, e.g. 51% in patients with septic shock as reported by Si Nga and colleagues[39].

Recovery from AKI was used to evaluate the potential benefit of Reltecimod, and efficacy was determined based on definition of full recovery, partial recovery or no recovery on Day 14 following Reltecimod drug administration.

Definitions were as follows:

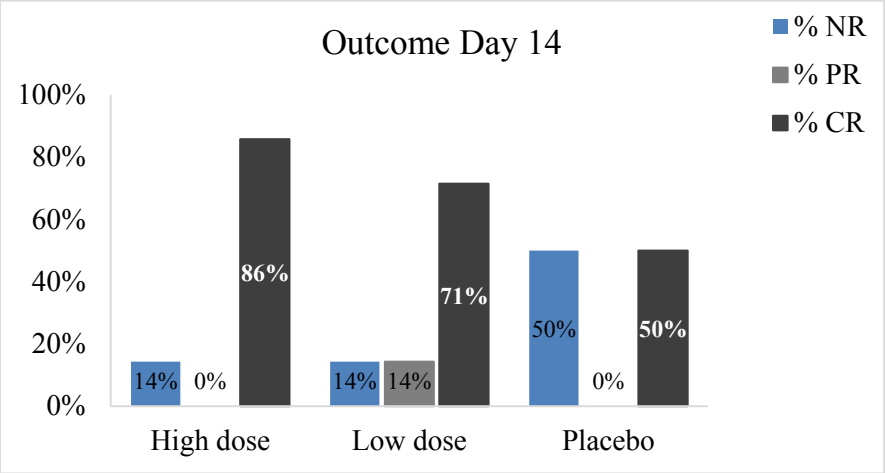
- **Complete recovery** was assumed if follow-up observed creatinine value(s) noted through Study Day 14 was <1.5 times the patient's reference creatinine.
- **Partial recovery** was assumed if a decrease in observed creatinine value(s) through Study Day 14 leading to a lower AKI stage (e.g. Stage 3 to Stage 2 or 1) but still with a final observed creatinine ≥1.5 times their pre-illness reference creatinine.
- **No recovery** was assumed if there was no change in AKI stage as assessed from the observed creatinine values available through Study Day 14 or the patient was receiving renal replacement therapy (RRT) at the time of last observed creatinine value(s) or patient death.

**Recovery from AKI:** Patients in the Reltecimod treatment groups experienced higher rates of complete recovery through Day 14 than the placebo group. Of the 7 patients treated with 0.50 mg/kg Reltecimod, 6 patients (86%) experienced complete recovery. Similar results were seen in the 0.25 mg/kg Reltecimod group, with complete recovery in 5 of the 7 patients (71%). On the other hand, only 2 of the 4 placebo-treated patients (50%) were completely recovered from AKI through Day 14. Of note, about 50% of spontaneous recovery is expected in this patient population, as observed in a retrospective clinical study of patients with NSTI[40].

The rates of no recovery were highest in the placebo group (50%), and comparably lower with Reltecimod (14% each in the high and low dose groups).

Recovery rates through Day 14 are illustrated by treatment group in Figure 4. Individual-patient data (including also baseline AKI stage) are presented in Table 3.

**Figure 4*:* AKI recovery rates through Day 14 by treatment group (Study ATX1002K)**




CR=complete recovery, NR=no recovery, PR=partial recovery.

**Table 3: Recovery from AKI through Day 14 by patient (Study ATX1002K)**

| 0.50 mg/kg Reltecimod (N=7) | | | 0.25 mg/kg Reltecimod (N=7) | | | Placebo (N=4) | | |
|---|---|---|---|---|---|---|---|---|
| **Patient No.** | **AKI Stage** | **Recovery Status** | **Patient No.** | **AKI Stage** | **Recovery Status** | **Patient No.** | **AKI Stage** | **Recovery Status** |
| 31006* | 1 | CR | 31007 | 2 | CR | 31002 | 3 | NR |
| 31014 | 2 | CR | 31010 | 2 | PR | 31029 | 2 | CR |
| 31034 | 2 | CR | 31015 | 1 | CR | 35001 | 2 | NR |
| 31039 | 1 | CR | 31019 | 3 | CR | 37004 | 1 | CR |
| 35003 | 1 | NR | 33003 | 1 | CR | | | |
| 37001 | 3 | CR | 33005* | 2 | NR | | | |
| 37007 | 1 | CR | 37006 | 2 | CR | | | |

AKI=acute kidney injury, CR=complete recovery, LOCF=last observation carried forward, N=number of subjects, NR=no recovery, PR=partial recovery.
AKI stage refers to stage at baseline

Individual-patient data indicate that complete recovery was not reserved to patients with mild AKI at baseline (KDIGO Stage 1) but was also observed in patients with more severe AKI (KDIGO Stage 2 or 3).

Patients were further followed using a biomarker for early renal damage, NGAL. NGAL is a sensitive and specific biomarker for early renal damage[41]. In agreement with NGAL being an early marker, Day 3 post-administration was chosen for the comparison of Reltecimod vs. placebo. This is supported by literature data from Di Somma et al.[42], showing that increased NGAL values are associated with AKI within the first 72 hours of hospitalization.

Results for NGAL are based on data from a subset of AKI patients (16 of the 18) considered for this post-hoc analysis.

NGAL levels are summarized by patient in Table 4.

**Table 4: NGAL levels (ng/mL) by patient (Study ATX1002K)**

| Treatment group Patient Number | NGAL Levels Day 0 | NGAL Levels Day 3 | AKI Recovery Status through Day 14 |
|---|---|---|---|
| **0.50 mg/kg Reltecimod** | | | |
| 31006 | 111 | 100 | CR |
| 31014 | 388 | 94 | CR |
| 31034 | 86 | 99 | CR |
| 31039 | 223 | 129 | CR |
| 37001 | 774 | 314 | CR |
| 37007 | 180[a] | 82 | CR |
| **0.25 mg/kg Reltecimod** | | | |
| 31007 | 271 | 106 | CR |
| 31010 | 139 | 114 | PR |
| 31015 | 211 | 117[b] | CR |
| 31019 | 321 | 140 | CR |
| 33003 | 143 | 103 | CR |
| 33005 | 712 | 164 | NR |
| 37006 | 102 | 34 | CR |
| **Placebo** | | | |
| 31002 | 100 | 106 | NR |
| 31029 | 820 | 230 | CR |
| 37004 | 463 (150[a]) | 93 | CR |

[a] Pre-surgery value
[b] Day 2 value
AKI=acute kidney injury, CR=complete recovery, NGAL= neutrophil gelatinase-associated lipocalin, NR=no recovery, PR=partial recovery.

Reductions in NGAL between Day 0 and Day 3 were seen in all patients, except for one patient in the placebo group (patient 31002) who did not recover from AKI, and for one patient in the high dose group (patient 31034), who recovered completely from AKI.

Reductions in NGAL levels were generally associated with favorable AKI recovery status, except for one patient in the 0.25 mg/kg group (patient 33005), who showed reduction in NGAL, but did not recover from AKI.

In light of the small patient numbers (especially in the placebo group) and the large variations in NGAL levels between subjects, a presentation of NGAL levels using mean and standard deviations would not be meaningful. Therefore, an alternative approach was used.

Values of around 90 ng/mL NGAL are reported to be "normal" levels[43]. In the literature, a cut-off of 150 ng/mL NGAL has been established as high sensitivity threshold for AKI prediction[42]. It is also the published 95th percentile of normal for the assay.

When using this cut-off, the rates of patients with NGAL values below 150 ng/mL on Day 0 were similar among Reltecimod- and placebo-treated patients (38.5% versus 33.3%).

However, on Day 3 a higher percentage of Reltecimod-treated patients had NGAL levels below 150 ng/mL (11 of 13 patients, 84.6%), compared to placebo-treated patients (2 of 3 patients, 66.7%), suggesting an improvement with Reltecimod.

## 4.2 Risks and Benefit

Patients randomized to receive placebo in addition to SoC intervention in the study will not benefit from the potential therapeutic effect of Reltecimod, however they stand to benefit from the safety measures and close observation included in the study as detailed below.

No compensation, monetary or otherwise is offered to study participants except to cover customary cost of travel and/or meals associated with any study required visits that may occur after hospital discharge.

Reltecimod has been evaluated in a set of toxicological and safety pharmacology studies. No dose limiting toxicities (DLTs) were detected in any of the animal toxicology studies, performed in mice, pigs, minipigs, and rabbits. The highest dose tested was 50 mg/kg, and based on the results of all studies, the apparent NOAEL is greater than 50 mg/kg.

In completed clinical studies, Reltecimod has been administered as a single intravenous infusion to 20 healthy subjects (at doses between 7.5 and 450 μg/kg), and to 32 NSTI patients (at doses of 0.25 or 0.50 mg/kg). In a fully-enrolled NSTI study (data blinded), Reltecimod has been administered as a single intravenous infusion to approximately 145 NSTI patients (dose 0.50 mg/kg) in ATB-202 without apparent safety concerns following unblinded review by an Independent Data Monitoring Committee (iDMC) for the first 200 randomized patients in that trial.

The single dose administration of Reltecimod was well tolerated in both study populations, and no specific drug-related concerns have been identified to date. Electrolyte abnormalities that were frequently seen in NSTI patients in ATB-201 are considered typical for this patient population.

Potential risks with CD28 antagonists include excessive pro-inflammatory response (measured by T cells activation and cytokine production) due to binding to CD28. In non-clinical studies, Reltecimod had no detectable agonist activity by itself, as no induction of interleukin-2 (IL-2), interferon-γ (IFN-γ) or tumor necrosis factor-α (TNF-α) was observed in human PBMCs after exposure to Reltecimod alone.

In clinical studies in healthy volunteers, administration of Reltecimod was shown to have no agonistic effect on various leukocytes subsets, as demonstrated by monitoring various lymphocytes subsets (CD4, CD3, CD8, Tregs, B cells) over time following Reltecimod administration. Both the percentage of positive cells and absolute counts remained similar to those at baseline.

Thus, the completed clinical studies as well as the ongoing study in NSTI did not raise any safety concerns.

Additionally, this study protocol details several safety measures

- Detailed exclusion criteria (Section 6.2) including:

- Any concurrent medical condition, which in the opinion of the Investigator, may compromise the safety of the patient or the objectives of the study or the patient will not benefit from treatment such as:
  - Congestive heart failure (CHF) {New York Heart Association (NYHA) class III-IV}
  - Very Severe chronic obstructive pulmonary disease (COPD) {GOLD Stage IV or use of continuous home oxygen prior to hospital admission (sleep apnoea treated with continuous positive airway pressure or biphasic positive airway pressure oxygen during sleep is acceptable)}
  - Liver dysfunction {Childs-Pugh class C}
  - Immunosuppression (see Appendix G for list of excluded immunosuppressive medications)
  - Known HIV infection with CD4 count < 200 cells/$mm^3$ or < 14% of all lymphocytes
  - Neutropenia < 1,000 cells/$mm^3$ not due to the underlying infection
  - Receiving or about to receive chemotherapy or biologic anti-cancer treatment, although hormonal manipulation therapies for breast and prostate malignancies are permitted
  - Hematological and lymphatic malignancies in the last 5 years
- Patient with >20% body surface area burn wounds
- Patient has acute pancreatitis with no established source of infection, uncomplicated appendicitis, or cholangitis or cholecystitis without peritonitis (necrotic or gangrenous gallbladder or appendix with peritonitis is allowed)
- Pregnant or breastfeeding women (lactating women must not breastfeed and must discard breastmilk for at least 28 days after receiving study drug); Women of childbearing potential must have a negative β-subunit hCG pregnancy test immediately prior to study entry.

- Frequent follow-up visits
- A medical monitor and iDMC will monitor the safety aspects of the study (see section 11.6).

Reltecimod will be investigated for treatment of SA-AKI in conjunction with SoC.

Proof of concept for use in this indication originates from a non-clinical study using a mouse model of sepsis-induced AKI, and from a post-hoc analysis of NSTI patients who developed AKI as part of their disease course. Efficacy data suggest a clinical benefit of Reltecimod with regard to recovery from AKI through 14 days post-administration.

Overall, the risk-benefit assessment is considered positive for investigation of Reltecimod in a clinical study in SA-AKI patients. The use of the established dose regimen (0.50 mg/kg Reltecimod as intravenous infusion) appears justified.

## 4.3 Study Treatment

This is a blinded randomized clinical study in which each patient will receive a single treatment of either 0.50 mg/kg Reltecimod or placebo (0.9% Sodium Chloride sterile solution) administered intravenously.

The intravenous infusion will be delivered by a syringe pump (may be manually pushed if approved by the medical monitor) over 10 minutes in a separate catheter than that used to deliver other medications. The syringe will identify the contents as "study drug" for protocol ATB-203. All study personnel and clinical staff, as well as the patient, shall remain blinded as to the actual composition of the study drug administered to a given patient. Only the assigned study pharmacist or authorized qualified designate (unblinded study-nurse/physician) preparing the drug shall be unblinded to the treatment.

### 4.3.1 Investigational Medicinal Product (IMP)

Reltecimod drug product is an injection, powder, lyophilized, for solution dosage form. It is formulated to contain 1 mg/mL of the Reltecimod peptide, 30 mg/mL mannitol, and 3.6 mg/mL sodium chloride after reconstitution with sterile WFI. The drug product to be used in clinical trials will be supplied in 20 mL vials. Each vial contains nominal amounts of the drug substance and excipients as follows: 10.5 mg of Reltecimod, 315 mg of mannitol, and 37.8 mg of NaCl.

Prior to use, each vial of drug product (containing 10.5 mg Reltecimod) is reconstituted in 10.5 mL of sterile WFI to generate a peptide concentration of 1 mg/mL. 10 mL of reconstituted solution (containing 10 mg Reltecimod) will be withdrawn from each vial and pooled together with 10 mL from additional reconstituted vials, to constitute the final amount (volume) of drug needed for each patient (based on individual patient's actual body weight).

The reconstituted drug product is administered directly and is not diluted prior to administration. The Reltecimod drug product will be administered as a single intravenous infusion at a dose of 0.50 mg/kg based on the patient's actual body weight. The drug product is infused over 10 minutes at a rate dependent on the dosing volume.

### 4.3.2 Comparator Product

The control product is 0.9% Sodium Chloride sterile solution administered as a single infusion at a volume based on the patient's actual body weight, 0.50 mL/kg (a volume equivalent with Reltecimod dosing schema). Placebo "study drug" will be administered intravenously over 10 minutes via syringe pump (may be manually pushed if approved by the medical monitor) in a manner similar to that used for the IMP.

## 4.4 Compliance Statement

This clinical study will be conducted according to the Declaration of Helsinki. The study will be conducted in compliance with this protocol, Good Clinical Practice (GCP) (CPMP/ICH/135/95), designated standard operating procedures (SOPs), and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

### 4.5 Study Population

Patients with

- Suspected or confirmed abdominal infection (planned or completed surgical (laparotomy or laparoscopy) or interventional radiologic procedures for control of underlying abdominal infection within 24 hours of evaluation by medical personnel); or surgically confirmed necrotizing soft tissue infection (NSTI)
- Requiring hospital admission to an intensive care unit (ICU) or step-down unit (or equivalent)
- Total Sequential Organ Failure Assessment (SOFA) score ≥2, and
- In whom the diagnosis of Stage 2 or 3 acute kidney injury (AKI; as defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria) is established at initial presentation for medical evaluation; or up to 48 hours from the suspected or confirmed diagnosis of abdominal infection or surgical confirmation of NSTI.

Patients will be stratified at time of randomization to two stratification variables:

- **Acuity of AKI:** whether or not AKI is diagnosed at time of presentation of abdominal infection or surgically confirmed NSTI; or during the 48 hours after the suspected diagnosis of abdominal infection or surgical confirmation of NSTI.
- **Subject Age:** ≥18 to ≤75 or >75 to ≤85 years old.

## 5. STUDY OBJECTIVES

### 5.1 Primary Objective

- To compare the rates of achieving the primary endpoint of freedom from durable loss of renal function (defined as alive, free of dialysis, and less than a 37% loss of estimated Glomerular Filtration Rate (eGFR; measured with the Modification of Diet in Renal Disease (MDRD) formula from the patient's reference eGFR)) at Day 28 between the Reltecimod- and placebo-treated patients
- To demonstrate the safety and tolerance of Reltecimod when administered as a single dose of 0.50 mg/kg to patients diagnosed with SA-AKI

### 5.2 Secondary Objectives

- To compare the rates of the primary endpoint at Day 14 between the Reltecimod- and placebo-treated patients.
- To compare time to the primary endpoint between the Reltecimod- and placebo-treated patients
- To compare AKI-free days over 14 and 28 days between the Reltecimod- and placebo-treated patients
- To compare the resolution of organ dysfunction (organ resolution is defined as having a SOFA score of ≤1 at Day 14, for individual organs and for total SOFA

score) between the Reltecimod- and placebo-treated patients over time and at Day 14

- To evaluate the effect of Reltecimod (compared to placebo-treated patients) in relation to the critical care and hospital stay parameters in patients with sepsis and AKI
  - Hospital length of stay
  - ICU length of stay
  - ICU free days in 28 days
  - Ventilator days
  - Ventilator free days in 28 days
  - Vasopressor days
  - Vasopressor free days in 28 days
  - RRT free days (days alive and free of RRT) in 28 days
- To compare survival status at Days 14 and 28 between the Reltecimod- and placebo-treated patients
- To tabulate the incidence of Stages 1, 2 and 3 AKI (using the KDIGO criteria) in patients with abdominal sepsis or NSTI
- To demonstrate the safety of Reltecimod in regard to susceptibility to secondary infections

### 5.3 Exploratory Objectives

- To compare the primary endpoint at Day 90 between the Reltecimod- and placebo-treated patients
- To compare the rates of improvement in durable loss of renal function (defined as alive, free of dialysis, and improvement leading to a lower AKI stage but no better than Stage 1 AKI) at Days 14, 28, and 90, between the Reltecimod- and placebo-treated patients
- To compare the distributions of acute kidney disease (AKD) stages (AKD 0, 1, 2, 3, and 3F) at Days 14 and 28 between the Reltecimod- and placebo-treated patients
- To conduct an exploratory evaluation of the incidence of CKD at Day 90
- To conduct an exploratory evaluation of survival status at Day 90 in the Reltecimod- and placebo-treated patients
- To conduct an exploratory evaluation of the primary endpoint by baseline pathogen
- To conduct an exploratory evaluation of RRT use (i.e., type of RRT)
- To evaluate the immunogenicity of Reltecimod
- To conduct an exploratory evaluation of plasma and urinary biomarkers in patients with AKI
- To conduct an exploratory evaluation of blood leukocyte transcriptome (RNA expression) profiling in patients with SA-AKI and compare genomic profile in patients treated with Reltecimod versus placebo
- To define potential surrogate biomarkers (systemic) that exhibit change from

baseline due to treatment with Reltecimod

## 5.4 Study Hypothesis

The clinical hypothesis of this study is that in addition to SoC, Reltecimod will demonstrate a clinically significant treatment benefit over placebo.

This hypothesis will be addressed by measuring the effect of Reltecimod in achieving freedom from durable loss of renal function in patients with sepsis due to abdominal infection or NSTI.

Specifically, the primary effectiveness hypothesis to be tested in this study is that in addition to SoC, the probability of durable loss of kidney function (defined as alive, free of dialysis and less than a 37% loss of eGFR (measured with the MDRD formula from the patient's reference eGFR)) at Day 28 will be larger among Reltecimod-treated patients compared to placebo-treated patients.

# 6. SELECTION OF STUDY POPULATION

To be enrolled in the study, patients must meet ALL of the inclusion criteria and NONE of the exclusion criteria.

## 6.1 Inclusion Criteria

1. Age: 18 up to and including 85 years.

2. Has either suspected or confirmed diagnosis of abdominal infection with planned or completed surgical (laparotomy or laparoscopy) or interventional radiologic procedures within 24 hours of evaluation by medical personnel, or surgically confirmed NSTI, requiring treatment with parenteral antibiotics. Recommended surgical or interventional radiologic procedures for abdominal infection be performed with 12 hours of evaluation by medical personnel.

   A. Abdominal Infection
   a. Suspected clinical diagnosis of abdominal infection as evaluated by the attending surgeon including any of the following clinical criteria
      - Abdominal pain and/or tenderness
      - Localized or diffuse abdominal wall rigidity
      - Mass
      - Ileus

   AND

      - Any of the following radiologic findings
        - Free air (Plain film, CT or MRI scans)
        - Intraabdominal abscess (ultrasound, CT or MRI scans)
        - Free peritoneal fluid (ultrasound, CT or MRI scans)

   OR

   b. Confirmed diagnosis of abdominal infection by any of the of the following criteria
      - Perforation and/or necrotic bowel with surgical confirmation of peritonitis
      - Presence of intraabdominal abscess by surgical confirmation or

drainage of purulent fluid from interventional radiologic procedure

OR

B. Necrotizing Soft Tissue Infection

- Surgical confirmation of NSTI by attending surgeon (e.g., presence of necrotic tissue, thrombosed vessels in the subcutaneous tissue, lack of bleeding and "dishwater" (cloudy, thin, gray) fluid due to presumed bacterial infection (necrotizing cellulitis (most commonly group A strep), necrotizing fasciitis, necrotizing myositis and myonecrosis, NSTI of the perineum, bacterial synergistic gangrene, Clostridial gas gangrene) that may be supported by specific signs and symptoms (e.g., tense edema outside area of compromised skin, pain disproportionate to appearance, skin discoloration, ecchymosis, blisters/bullae, necrosis,, crepitus, and or subcutaneous gas).

3. SOFA score ≥2 (in any one or combination of the 6 major components of the SOFA score), measured as close as possible to study drug administration (but before study drug is administered).

4. Planned or current admission to an ICU or step down unit (or equivalent).

5. Initial diagnosis of AKI established either upon presentation to medical care at the study site in those patients with suspected or confirmed abdominal infection or surgically confirmed NSTI; or in those patients in whom the initial diagnosis of AKI is established during the 48-hour period from the suspected or confirmed diagnosis of abdominal infection or surgical confirmation of NSTI.

   AKI Stage 2 or 3 according to the following KDIGO AKI criteria:

   a. Stage 2 AKI

      i. Increase in serum creatinine to ≥ 200% (≥ 2.0–fold) from a reference creatinine value (see below) in the absence of primary underlying renal disease (eGFR >30 mL/min)

         OR

      ii. Urine output < 0.5 mL/kg/hr x 12 hours following adequate fluid resuscitation [the aggregate over any 12-hour period can be used with hourly rate being relatively persistent over the 12-hour period]

         Urine output should be calculated using Ideal Body Weight (IBW; using the Miller Formula[52])

   b. Stage 3 AKI

      i. Increase in serum creatinine to ≥ 300% (≥ 3.0–fold) from a reference creatinine value in the absence of primary underlying renal disease (eGFR >30 mL/min)

         OR

      ii. Serum creatinine ≥4 mg/dL

         OR

      iii. Planned or initiation of RRT for acute AKI

- Order for RRT must be in place
- RRT may be started prior to study drug administration as long as the patient is off RRT during study drug administration and up to at least one hour post study drug administration

OR

iv. Urine output < 0.3 mL/kg/hr x 24 hours or anuria x 12 hours following adequate fluid resuscitation

- Urine output should be calculated using IBW (using the Miller Formula)

The reference creatinine value is the serum creatinine value according to the following order:

i. Value within 3 months of the hospital admission
   - If single value available, then use the single value for reference
   - If two values available, then use the average of two values for reference
   - If three or more values available, then use the median of the three most recent values for reference

ii. Value between 3 and 12 months prior to hospital admission
   - If single value available, then use the single value for reference
   - If two values available, then use the average of two values for reference
   - If three or more values available, then use the median of the three most recent values for reference

iii. At hospital admission (if the patient is admitted without an acute illness)

c. Patients without a reference creatinine value would also be considered to have Stage 2 or 3 AKI if they have a serum creatinine ≥ 200% (≥ 2.0-fold) the normal creatinine value for age, race, and gender (Appendix F) and a renal ultrasound (US) or computed tomography (CT) showing normal kidney size within the past 90 days. Normal kidney size is defined as

i. Computed Tomographic Scan

ii. If either kidney is ≥9 cm length

iii. Renal Ultrasound[54]
   - <60 years if either kidney is ≥10 cm length
   - ≥60 years if either kidney is ≥9.5 cm length

6. Study medication must be administered within 6 hours of confirmation of onset of Stage 2 or 3 AKI as established at the study site, under the following criteria

- After the decision is made by the attending surgeon at the study site for a surgical or interventional radiology procedure for the abdominal infection

OR

- After confirmed diagnosis of abdominal infection has been established by a surgical or interventional radiology procedure

  OR

- After surgical confirmation of NSTI

7. Females of childbearing potential must consistently use an acceptable method of contraception from baseline through Day 28. Females of childbearing potential must have a negative β-subunit hCG pregnancy test (urine or blood whichever if faster; blood only in France) immediately prior to study entry.

   - Non-childbearing potential is defined as current tubal ligation, hysterectomy, or ovariectomy or post-menopause (1 year without menses with an appropriate clinical profile at the appropriate age e.g. >45 years).
   - Acceptable methods of contraception for this study is defined as abstinence, hormonal therapy (e.g., oral contraceptives, hormone implants), intra-uterine (IUD) device, diaphragm with spermicide, condom with spermicide.

8. If a male patient's sexual partner is of childbearing potential, the male patient must acknowledge that they will consistently use an acceptable method of contraception (defined above) from baseline through Day 28.

9. Signed and dated informed consent form (ICF) as defined by the institutional review board (IRB) or Ethics Committee (EC) and, if applicable, California Bill of Rights. By signing the ICF, the patient agrees to release any medical records pursuant to current Health Insurance Portability and Accountability Act (HIPAA) Guidelines or to local country privacy regulations. If patient is unable to comprehend or sign the ICF, patient's legally acceptable representative (or an independent physician if allowed by local rules and regulations) may sign the ICF.

## 6.2 Exclusion Criteria

1. Has known prior history of CKD with a documented eGFR < 30 mL/min by a commonly used formula such as MDRD or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), or known GFR < 30 mL/min.
   a. Exception: Patients with history of CKD but no available prior eGFR who have documented normal kidney size on ultrasound or computed tomography (normal size defined above) evaluation (performed within 90 days of screening) will be eligible

2. Patients receiving RRT for chronic kidney disease: either hemodialysis, peritoneal dialysis, hemofiltration such as Continuous Veno-Venous Hemofiltration (CVVH) or hemodiafiltration.

3. Previously diagnosed with documented AKI in the last 30 days.

4. Documented primary glomerular disease or toxic tubulo-interstitial nephritis or other underlying renal diseases significantly effecting renal function (e.g., renal amyloidosis, polycystic kidney disease, renal cancer, renal abscess) at the time of AKI diagnosis.

5. Patients with overt peripheral vascular disease in the involved NSTI area - associated with ischemic wounds/ulcers or gangrene, and/or other significant symptoms of inadequate vascular supply or where limb amputation is considered likely within 7 days due to the peripheral vascular disease.

6. Diabetic patients with peripheral vascular disease who present with below the ankle NSTI.

7. Current condition of
   (a) Inability to maintain a mean arterial pressure > 50 mmHg and/or systolic blood pressure > 70 mmHg for at least 1 hour prior to dosing despite the presence of vasopressors and IV fluids, or
   (b) a patient with respiratory failure such that an $SaO_2$ of 80% for at least 1 hour prior to dosing cannot be achieved, or
   (c) a patient with refractory coagulopathy (INR >5) or thrombocytopenia (platelet count <20,000) that does not partially correct for at least 1 hour prior to dosing with administration of appropriate factors or blood products

8. Severe neurological impairment due to cerebrovascular accident or cardiac arrest.

9. Recent cerebrovascular accident in the last 3 months.

10. Patients with cardiac arrest requiring cardiopulmonary resuscitation within the past 30 days.

11. Patient is not expected to survive throughout 28 days of study due to underlying medical condition, such as poorly controlled neoplasm (e.g. Stage III or IV cancer).

12. Classified as "Do Not Resuscitate", or "Do Not Treat", or the patient's family is not committed to aggressive management of the patient's condition. A "no cardiopulmonary resuscitation (CPR)" order is acceptable if the patient and/or the family are still committed to aggressive care short of CPR.

13. Any concurrent medical condition, which in the opinion of the Investigator, may compromise the safety of the patient or the objectives of the study or the patient will not benefit from treatment such as
    - Congestive heart failure (CHF) {New York Heart Association (NYHA) class III-IV}
    - Very severe chronic obstructive pulmonary disease (COPD) {GOLD Stage IV or use of continuous home oxygen prior to hospital admission (sleep apnoea treated with continuous positive airway pressure or biphasic positive airway pressure oxygen during sleep is acceptable)}
    - Liver dysfunction {Childs-Pugh class C}
    - Primary or acquired immunodeficiency or immunosuppression due to treatment with immunosuppressive medications (see Appendix G for list of excluded immunosuppressive medications)
    - Known HIV infection with CD4 count < 200 cells/$mm^3$ or < 14% of all lymphocytes
    - Neutropenia < 1,000 cells/$mm^3$ not due to the underlying infection
    - Receiving or about to receive chemotherapy or biologic anti-cancer

treatment, although hormonal manipulation therapies for breast and prostate malignancies are permitted
- Hematological and lymphatic malignancies in the last 5 years

14. Patient with >20% body surface area burn wounds.

15. Patient has acute pancreatitis with no established source of infection, uncomplicated appendicitis, or cholangitis or cholecystitis. Note - necrotic or gangrenous gallbladder or appendix with peritonitis is allowed.

16. Pregnant or breastfeeding women (lactating women must not breastfeed and must discard breastmilk for at least 28 days after receiving study drug); Women of childbearing potential must have a negative β-subunit hCG pregnancy test immediately prior to study entry.

17. Previous enrollment in a clinical trial involving investigational drug or a medical device within 30 days before provision of written informed consent for the study or within five half-lives of the investigational drug, whichever is longer.

18. Previous enrollment in any Reltecimod protocol (ATB-001, ATB-201, ATB-202 or ATB-203).

19. Patients under guardianship or trusteeship (France only).

20. Absence of social insurance (France only).

## 6.3 Withdrawal

Patients will be informed that they are free to withdraw from the study at any time and for any reason. The date the patient is withdrawn from the study and the reason for withdrawal will be recorded in the eCRF and in the source documentation.

Whenever possible, all patients who discontinue study treatment or withdraw from the study prematurely will undergo all end-of-study assessments. Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol.

It is vital to obtain follow-up data on any patient withdrawn because of an AE or SAEs. In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

The reason for withdrawal of a patient must be recorded on the eCRF, if it can be ascertained. Any further treatment will be at the Investigator's discretion and should be recorded. Every effort must be made to follow-up the patient and obtain information on clinical outcome and AEs. All data from withdrawals will be included in the safety analysis.

### 6.3.1 Criteria for Premature Discontinuation from Study

In rare instances, the patient (or Investigator) may determine that he/she is not able to make all visits required by the protocol. Possible reasons for discontinuation from the study may include:

- Withdrawal of consent
- Lost to follow-up
- Other reasons such as administrative reasons

# 7. INVESTIGATIONAL PLAN

## 7.1 Dose Selection Rationale

The formulation in the two completed clinical studies (ATB-001, ATB-201) and the ongoing clinical study with Reltecimod (ATB-202) is identical to the formulation used in this clinical study in patients with SA-AKI (ATB-203). Reltecimod will be dosed according to the patient's actual body weight, at 0.50 mg/kg, and will be administered as an intravenous infusion over 10 minutes.

The rationale for the proposed dose in the planned SA-AKI study is based on data from the Phase 2 study in NSTI. In this study with two Reltecimod dose groups (0.25 and 0.50 mg/kg), evidence for a dose response was seen across multiple domains of efficacy variables. A linear dose response emerged for individual endpoints such as: SOFA score (measured either as total score at Day 14, individual organ score at Day 14, change in total score between days 1-14, percent of patients with organ failure at Day 14, SOFA score over time in patients presenting with organ failure at Day 1), debridements (measured as number of debridements to Day 7 or 28, percent of patients needing only one debridement, percent of patients needing less than 4 debridement to resolve the infection), and response of inflammatory biomarkers (measured systemically in plasma and at the tissue level from the site of infection).

Overall, these results suggest that the 0.50 mg/kg dose is superior to the 0.25 mg/kg dose regarding efficacy in NSTI patients. The safety profile was similar for the two Reltecimod doses. Thus, the 0.50 mg/kg dose was chosen for further clinical studies. This dose was shown to be efficacious in the post–hoc analysis of NSTI patients with AKI. The 0.50 mg/kg dose provided the highest treatment benefit in these patients, as judged by the rate of complete recovery from AKI. Thus, it was chosen for further studies in patients with SA-AKI.

## 7.2 Allocation of Treatment, Randomization and Study Drug Administration

The pharmacist (or unblinded study-nurse/physician if performing study drug preparation at individual institution) will get the treatment allocation via fax and email notification after randomization in the RAVE™ EDC by site personnel available only to the study pharmacist (or unblinded study-nurse/physician if performing study drug preparation at individual institution). All other study-related personnel, hospital care givers, the Sponsor and the patient will remain blinded.

Following allocation of treatment, the study pharmacist (or unblinded study-nurse/physician if performing study drug preparation at individual institution) will prepare the study drug.

## 7.3 Schedule of Procedures/Visits

A schedule of study assessments is shown in Section 18-Appendix A ("Study Visits and Procedures") of the protocol. Homecare services will be offered through a third party vendor (i.e., Symphony Clinical Research) using trained, qualified homecare professionals. Provision of this service is intended to help ensure patient retention and data collection when travel to the clinical trial sites may be overly burdensome for the participants given their disease state. Symphony Clinical Research is contracted to evaluate subjects as outpatients from Day 7 through Day 90.

Local laboratories will be used during hospitalization and clinic visits while the home health service will send samples to a central laboratory. Outpatient samples may be evaluated by other local laboratories if acceptable accreditation.

Patients who are registered and randomized for the study, but do not receive study drug (part of the Intent-to-Treat (ITT) population) should continue to be followed through Day 90 with as much data collected as part of SOC entered into the eCRF. No additional procedures or laboratory studies should be performed beyond SOC as part of the research study. The entered data will match as closely as possible the SoC assessments and laboratory evaluations with the visit days.

**Visit 1: Screening**

Evaluation starts once a patient presents with clinical diagnosis of abdominal infection.

- Obtain ICF
- Verification of Inclusion/Exclusion criteria
- Demographics, medical history, infection history, concomitant medications, vital signs, height, weight, physical exam (PE). Race is not entered for European countries.
- Record urine output from presentation or around (before) time of diagnosis of abdominal infection or NSTI recorded to study drug administration or until 48 hour window to develop Stage 2 or 3 AKI ends
- Record serum creatinine values every 6 hours from presentation or around (before) time of diagnosis of abdominal infection until study drug administration or until 48 hour window to develop Stage 2 or 3 AKI ends (blood draws may be adjusted to when blood is normally collected on the unit)
- Determine kidney size by CT or renal ultrasound if patient does not have a reference creatinine value within the past 12 months
- Recording baseline signs and symptoms and AEs/SAEs (AEs of Screening are AEs/ SAEs starting after obtaining ICF until study drug administration)
- Safety baseline laboratory tests:
  - Full chemistry panel (see Section 9.2.11)
  - Complete blood count (CBC) with differential and platelet count
- Spot urine for albumin to creatinine ratio
- Standard C-reactive protein (CRP)

- Arterial blood gas and FiO2 (if applicable) or SpO2 and FiO2 if arterial blood gas is not clinically indicated
- Blood culture for both aerobic and anaerobic bacteria
- Pregnancy test if applicable (blood or urine whichever is faster; blood only in France)
- Screening SOFA score will include measurements must be performed prior to study drug administration: SOFA score should be evaluated any time after arrival at the hospital (may include data from referring hospital), although no more than 6 hours prior to study drug administration. Baseline SOFA score will include the following organ/systems (with the total score being at least a 2): respiratory, cardiovascular, renal, coagulation, GI/hepatic and CNS.
- APACHE II score (measurement for this score will be collected and the score will be calculated retrospectively) using the worst values within the 24-hour period prior to enrollment
- Critical care parameters (dates and times of assisted ventilation, vasopressor use, ICU and hospital admission and discharge)
- Collect data on acute RRT
- Record additional relevant procedures related to the kidney (e.g., renal biopsy)
- Record any imaging that evaluates the kidney
- Local lesion assessment and evidence of amputation (excision to a joint space) if NSTI
- During surgery, peritoneal or abscess fluid, abdominal tissue samples, or NSTI tissue samples for microbiology
- Collect blood for serum for storage (immunogenicity testing)
- Collect urine and blood for plasma for storage (AKI biomarker analysis) – optional sub-study
- Collect blood for systemic inflammatory biomarkers – leukocyte transcriptome (RNA expression) profiling and chemokines / cytokines – optional sub-study
- Record Survival
- Perform randomization and study drug preparation if patient has confirmed diagnosis of Stage 2 or 3 AKI
    - Patients with suspected or confirmed abdominal infection or surgically confirmed NSTI who do not meet AKI criteria at time of abdominal infection presentation or surgical confirmation of NSTI should be followed every 6 hours with a repeat creatinine test and monitoring of urine output every 1 to 6 hours, for up to 48 hours after the suspected diagnosis of abdominal infection or surgical confirmation of NSTI, to determine if they develop Stage 2 or 3 AKI
- Upon study drug administration patient is transitioned to Visit 2 (Day 1)

**Visit 2 (Day 1)**

Starts only upon study drug administration and terminates at the end of the calendar day. For abdominal sepsis, study drug may be given prior to, during, or after surgery if meets

all criteria. For NSTI, study drug may only be given during surgery or immediately after surgery (after surgical confirmation of NSTI).

- Drug (to be infused over 10 minutes) should be administered within 6 hours, under the following criteria, whichever is later, (as described in inclusion criteria Section 6.1):
    - After confirmation of Stage 2 or 3 AKI as established at the study site

    AND

    A. Abdominal Infection

    - After the decision is made by the attending surgeon at the study site for a surgical or interventional radiology procedure for the abdominal infection
      OR
    - After confirmed diagnosis of abdominal infection has been established by a surgical or interventional radiology procedure

    OR

    B. Necrotizing Soft Tissue Infection

    - After surgical confirmation of NSTI (drug should not be administered until surgical confirmation of NSTI is established)

    Note: If a surgical or interventional radiology procedure for the abdominal infection, or surgical confirmation of NSTI, occurred at an outside hospital prior to transfer to the study site, study medication must be administered within 6 hours of re-established diagnosis of Stage 2 or 3 AKI at the study site.
- Record if overdose
- Record any follow-up surgical or interventional radiologic procedures for previously documented abdominal infection or NSTI
- Collection of AEs/ SAEs
- Concomitant medications
- Vital signs (first set of vitals on that day)
- Symptom-driven interim PE
- Fluid balance (total in/out-I/O) for calendar day starting from the time accurate I/Os recorded (start time may be prior to study drug administration)
- Detailed urine output
    - Should be recorded continuously from time of study drug administration to Day 7 (if still in ICU or step down unit), using most frequent hourly intervals available and by calendar day with or without Foley catheter in place
- Spot urine for albumin to creatinine ratio
- Collect data on acute RRT
- Record additional relevant procedures related to the kidney (e.g., renal biopsy)
- Record any imaging that evaluates the kidney
- Weight, only if not collected at screening
- Collect data on additional amputations if NSTI

- Critical care parameters (dates and times of assisted ventilation, vasopressor use, ICU /hospital stay)
- Systemic response: SOFA score.
  - All efforts should be made to obtain the actual measurements of SOFA parameters at these visits - may use SpO2 value (and record FiO2) if arterial blood gas is not clinically indicated
  - Obtain serum creatinine and total bilirubin
  - Obtain CBC with differential and platelet count
- Assess lesion status if NSTI (healing/progression/significant change in appearance) if accessible for visible assessment at time of debridement or routine dressing change
- Collect blood for systemic inflammatory biomarkers – leukocyte transcriptome (RNA expression) profiling and chemokine / cytokines at 4-6 hours post study drug administration – optional sub-study
- Survival

**Visit 3 (Day 2)**

- Fluid balance (total I/O) for calendar day
- Detailed urine output
  - Should be recorded continuously from time of study drug administration to Day 7 (if still in ICU or step down unit), using most frequent hourly intervals available and by calendar day, with or without Foley catheter in place
- Collect data on additional amputations if NSTI
- Collect data on acute RRT
- Record additional relevant procedures related to the kidney (e.g., renal biopsy)
- Record any imaging that evaluates the kidney
- Collection of AEs/ SAEs
- Record any follow-up surgical or interventional radiologic procedures for previously documented abdominal infection or NSTI
- Concomitant medications
- Vital signs (to be taken during the morning tests)
- Serum creatinine
- Critical care parameters (dates and times of assisted ventilation, vasopressor use, ICU /hospital stay)
- Assess lesion status if NSTI (healing/progression/significant change in appearance) if accessible for visible assessment at time of debridement or routine dressing change
- Collect urine and blood for plasma for storage (AKI biomarker analysis) at 24±6 hours after study drug administration – optional sub-study
- Collect blood for systemic inflammatory biomarkers - leukocyte transcriptome (RNA expression) profiling and chemokine / cytokines at 24±4 hours post study drug administration – optional sub-study
- Record Survival

**Visit 4 (Day 3)**

- Fluid balance (total I/O) for calendar day
- Detailed urine output
  - Should be recorded continuously from time of study drug administration to Day 7 (if still in ICU or step down unit), using most frequent hourly intervals available and by calendar day with or without Foley catheter in place
- Collect data on additional amputations if NSTI
- Collect data on acute RRT
- Record additional relevant procedures related to the kidney (e.g., renal biopsy)
- Record any imaging that evaluates the kidney
- Collection of AEs/ SAEs including secondary infections
- Record any follow-up surgical or interventional radiologic procedures for previously documented abdominal infection or NSTI
- Concomitant medications
- Vital signs (to be taken during the morning tests)
- Symptom-driven interim PE
- Evaluation of adequacy of antimicrobial treatment, based on results from susceptibility testing once the data is available
- Critical care parameters (dates and times of assisted ventilation, vasopressor use, ICU /hospital stay)
- Systemic response: SOFA score (measurements will be collected, and scores will be calculated retrospectively)
  - All efforts should be made to obtain the actual measurements of SOFA parameters at these visits - may use SpO2 value (and record FiO2) if arterial blood gas is not clinically indicated
  - Obtain serum creatinine and total bilirubin
  - Obtain CBC with differential and platelet count
- Assess lesion status if NSTI (healing/progression/significant change in appearance) if accessible for visible assessment at time of debridement or routine dressing change
- Spot urine for albumin to creatinine ratio
- Collect blood for systemic inflammatory biomarkers - leukocyte transcriptome (RNA expression) profiling and chemokine / cytokines at 48$\pm$4 hours post study drug administration – optional sub-study
- Record Survival

**(Days 4 to 6)**

- Fluid balance (total I/O) for calendar day
- Detailed urine output
  - Should be recorded continuously from time of study drug administration to Day 7 (if still in ICU or step down unit), using most frequent hourly intervals available and by calendar day with or without Foley catheter in place

- Collect data on additional amputations if NSTI
- Collect data on acute RRT
- Record additional relevant procedures related to the kidney (e.g., renal biopsy)
- Record any imaging that evaluates the kidney
- Collection of AEs/ SAEs including secondary infections
- Record any follow-up surgical or interventional radiologic procedures for previously documented abdominal infection or NSTI
- Concomitant medications
- Critical care parameters (dates and times of assisted ventilation, vasopressor use, ICU /hospital stay)
- Collect blood for systemic inflammatory biomarkers - leukocyte transcriptome (RNA expression) profiling and chemokine / cytokines at 72±4 hours post study drug administration – optional sub-study (Day 4 only)
- Record survival

**Visit 5 (Day 7 [±1 day])**

- Fluid balance (total I/O) for calendar day
- Detailed urine output
  - Should be recorded continuously from time of study drug administration to Day 7 (if still in ICU or step down unit (or equivalent), using most frequent hourly intervals available and by calendar day with or without Foley catheter in place
- Collect data on additional amputations if NSTI
- Collect data on acute RRT
- Record additional relevant procedures related to the kidney (e.g., renal biopsy)
- Record any imaging that evaluates the kidney
- Weight (if easily obtained)
- Collection of AEs/ SAEs including secondary infections
- Record any follow-up surgical or interventional radiologic procedures for previously documented abdominal infection or NSTI
- Concomitant medications
- Vital signs (to be taken during the morning tests)
- PE (visiting nursing service does not perform if outpatient)
- Standard CRP
- Spot urine for albumin to creatinine ratio
- Safety laboratory tests
  - Full chemistry panel (see Section 9.2.11)
  - CBC with differential and platelet count
- Critical care parameters (dates and times of assisted ventilation, vasopressor use, ICU /hospital stay)
- Record any hospital re-admissions (if previously discharged for original sepsis-related hospitalization)

- Systemic response: collect data for SOFA parameters
  - All efforts should be made to obtain the actual measurements of SOFA parameters at these visits-may use SpO2 value (and record FiO2) if arterial blood gas is not clinically indicated.
  - Platelet count, creatinine and total bilirubin values required for SOFA components can be obtained from safety laboratories performed at this visit.
- Assess lesion status if NSTI (healing/progression/significant change in appearance) if accessible for visible assessment at time of debridement or routine dressing change
- Collect urine and blood for plasma for storage (AKI biomarker analysis) – optional sub-study
- Record Survival

**Visit 6 (Day 10 [±1 day]; perform only if patient is still hospitalized)**

- Concomitant medications
- Collection of AEs/SAEs, including secondary infections
- Collect data on additional amputations if NSTI
- Collect data on acute RRT
- Record additional relevant procedures related to the kidney (e.g., renal biopsy)
- Record any imaging that evaluates the kidney
- Record any follow-up surgical or interventional radiologic procedures for previously documented abdominal infection or NSTI
- Symptom-driven interim PE
- Vital signs (to be taken during the morning tests)
- Critical care parameters (dates and times of assisted ventilation, vasopressor use, ICU /hospital stay)
- Record any hospital re-admissions (if previously discharged for original sepsis-related hospitalization)
- Serum creatinine
- Assess lesion status if NSTI (healing/progression/significant change in appearance) if accessible for visible assessment at time of debridement or routine dressing change
- Record Survival

**Visit 7 (Day 14 [±1 day])**

- Weight
- Collection of AEs/SAEs, including secondary infections
- Collect data on acute RRT
- Record additional relevant procedures related to the kidney (e.g., renal biopsy)
- Record any imaging that evaluates the kidney
- Record any follow-up surgical or interventional radiologic procedures for previously documented abdominal infection or NSTI
- Concomitant medications

- Safety laboratory tests (Chemistry, Hematology)
  - Full chemistry panel (see Section 9.2.11)
  - CBC with differential and platelet count
- Spot urine for albumin to creatinine ratio
- PE (visiting nursing service does not perform if outpatient)
- Vital signs (to be taken during the morning tests if still hospitalized)
- Standard CRP
- Collect blood for serum for storage (immunogenicity testing)
- Critical care parameters (dates and times of assisted ventilation, vasopressor use, ICU /hospital stay)
- Record any hospital re-admissions (if previously discharged for original sepsis-related hospitalization)
- Systemic response: collect data for SOFA parameters
  - All efforts should be made to obtain the actual measurements of SOFA parameters at these visits-may use SpO2 value (and record FiO2) if arterial blood gas is not clinically indicated.
  - Platelet count, creatinine and total bilirubin values required for SOFA components can be obtained from safety laboratories performed at this visit.
  - In case a patient is discharged from hospital prior to these days SOFA parameters should be obtained on the same day of discharge.
- Assess lesion status if NSTI (healing/progression/significant change in appearance) if accessible for visible assessment at time of debridement or routine dressing change
- Record Survival

**Visit 8 (Day 21 [±1 day])**

- Collection of AEs/SAEs, including secondary infections
- Collect data on additional amputations if NSTI
- Collect data on acute RRT
- Record additional relevant procedures related to the kidney (e.g., renal biopsy)
- Record any imaging that evaluates the kidney
- Concomitant medications
- Critical care parameters (dates and times of assisted ventilation, vasopressor use, ICU /hospital stay)
- Record any hospital re-admissions (if previously discharged for original sepsis-related hospitalization)
- Vital Signs (to be taken during the morning tests if still hospitalized)
- Serum creatinine
- Record Survival

**Visit 9 (Day 29 [+3 days])**

- Weight
- Collection of AEs/SAEs, including secondary infections

- Collect data on acute RRT
- Record additional relevant procedures related to the kidney (e.g., renal biopsy)
- Record any imaging that evaluates the kidney
- Collect data on additional amputations if NSTI
- Concomitant medications
- Critical care parameters (dates and times of assisted ventilation, vasopressor use, ICU /hospital stay)
- Vital signs (to be taken during the morning tests if still hospitalized)
- Serum creatinine and albumin
- CBC with differential and platelet count
- Standard CRP
- Spot urine for albumin to creatinine ratio
- Collect blood for serum for storage (immunogenicity testing)
- Record any hospital re-admissions (if previously discharged for original sepsis-related hospitalization)
- Record Survival

All efforts should be made to collect these data, especially laboratory data, with Day 28 being the primary endpoint, but in case parameters cannot be collected, phone follow-up will be performed, and information that could be collected over the phone will apply.

**Visit 10 (3 to 21 Days after Visit 9)**

- Serum creatinine

**Visit 11 (Day 90 [+5 days])**

The 3-month visit is a follow-up visit to assess the long-term health condition of the patients including assessment of

- Serum creatinine
- Spot urine for albumin to creatinine ratio
- Serum for storage (immunogenicity test)
- Record survival
- Record any hospital readmission(s) within 30 days of discharge from original sepsis-related hospitalization.

**Follow-up of Patients**

Patients who received the study drug are required to complete the procedures outlined for this clinical study. Exceptions would only include the withdrawal of consent, lost to follow-up or death.

If a patient misses a scheduled visit, attempts to complete the patient data will be made via telephone or rescheduling the visit. After waiting one week for the response, a return-receipt, certified letter containing instructions to call for an appointment will be sent. If no response is obtained within one week after sending the return-receipt letter, the patient should then be considered as lost to follow-up. The returned receipt should be filed in the

Investigator's regulatory binder to document the site's attempt to arrange patient follow-up. A clinical evaluation should be made based on the last contact with the patient.

SAEs occurring within 28 days of a patient receiving IMP will be recorded and processed as described in Section 11.3 of the protocol.

# 8. TREATMENT OF PATIENTS

## 8.1 Investigational Medicinal Product

This is a blinded randomized clinical study with two treatment groups consisting of 0.50 mg/kg Reltecimod and placebo. Patients will be randomized in a 1:1 ratio. Each patient will be administered a single intravenous infusion of Reltecimod based on actual body weight to be infused over 10 minutes at a rate dependent on the dosing volume. Volume of administration will depend on the patients' actual body weight.

The study drug should be administered within 6 hours of the laboratory confirmed diagnosis of Stage 2 or 3 AKI as established at the study site, only after the decision is made by the attending surgeon at the study site for a surgical or interventional radiology procedure for the abdominal infection or after confirmed diagnosis of abdominal infection has been established by a surgical or interventional radiology procedure; or after surgical confirmation of NSTI as described in the inclusion criteria (Section 6.1).

Reltecimod will be supplied in glass vials as a lyophilized powder to be reconstituted with sterile WFI. Drug will be reconstituted on the day of its administration, in close proximity to infusion time, and several vials will be pooled together to compose the requested dose. Final volume for infusion will be based on the patient's actual body weight plus adequate priming volume of the IV line.

Placebo will be pyrogen-free, preservative-free sterile 0.9% saline, USP administered as a single infusion at a volume calculated and based on the patient's actual body weight, 0.50 mL/kg (a volume equivalent with Reltecimod dosing schema), plus adequate priming volume of the IV line.

### 8.1.1 Presentation and Formulation

Reltecimod is the sodium salt of a 10 amino acid synthetic peptide. Reltecimod has homology to amino acid residues 8-15 of the T-lymphocyte molecule CD28 and has D-Ala residues abutted to N- and C-termini to render them more protease resistant. The final formulated drug product is a lyophilized powder, formulated to contain 1 mg/mL of the Reltecimod peptide, 30 mg/mL mannitol, and 3.6 mg/mL sodium chloride after reconstitution with sterile WFI.

The drug product is filled into clear, 20 mL Type I glass vials with a 20 mm neck and is then lyophilized. Flurotec-coated rubber lyophilization stoppers are used and 20 mm white aluminum overseals.

Each vial of drug contains nominal amounts of the drug substance and excipients as follows: 10.5 mg of Reltecimod, 315 mg of mannitol, and 37.8 mg of NaCl. Prior to use,

each vial of drug product (10.5 mg Reltecimod) is reconstituted in 10.5 mL of water for injection to generate a peptide concentration of 1 mg/mL.

The reconstituted drug product is administered directly and is not diluted prior to administration. To prepare the drug quantity needed for infusion, the contents of several vials are pooled together by the study pharmacist (or unblinded study-nurse/physician if performing study drug preparation at individual institution), under sterile conditions. The number of vials would depend on the patient's actual body weight, in order to achieve a dose of 0.50 mg/kg. The Reltecimod drug product will be administered at a dose of 0.50 mg/kg via a syringe pump (may be manually pushed if approved by the medical monitor) in a separate catheter as a single intravenous infusion given over 10 minutes.

The manufacturer of the clinical batches of the drug substance is PolyPeptide Laboratories, Inc., Torrance CA. The manufacturer of the drug product is Emergent BioSolutions Inc, Baltimore, MD.

### 8.1.2 Storage

IMP will be stored in a limited access area, under appropriate environmental conditions. Reltecimod should be stored at -20°C ± 5°C in a secure, temperature-monitored freezer located in Investigational Drug Service or main pharmacy. Reconstituted investigational agents may be stored at room temperature for up to 6 hours. Study drug infusion should be performed as soon as possible but within the 6-hour window previously described. If reconstituted drug is not administered, it should be discarded.

### 8.1.3 Administration

Formulation and/or preparation of Reltecimod or placebo will be performed by the clinical site pharmacist (or unblinded study-nurse/physician if performing study drug preparation at individual institution). This process will be performed so that the clinical staff and Investigators will be blinded to each patient’s treatment assignment and only the pharmacist (or unblinded study-nurse/physician if performing study drug preparation at individual institution) will be unblinded. Administration will be by intravenous infusion using a syringe pump (may be manually pushed if approved by the medical monitor) over a 10-minute period. RRT may be started prior to study drug administration as long as the patient is off RRT during study drug administration and up to at least one hour post study drug administration.

### 8.1.4 Accountability and Destruction of Surplus Investigational Product

Authorization of the site to receive supplies of IMP will be given by Atox Bio/designee upon receipt of relevant essential documentation (for details refer to the Study Procedure Manual). A designated individual at each site will maintain a log of IMP dispensed for each patient. In addition, the Investigator or designated individual at each site will maintain an IMP Accountability Log. This will include the description and quantity of IMP received at the study site, as well as a record of when and to whom it was dispensed.

All used and unused supplies will be retained at the investigational site until the study monitor gives instructions for their disposal or return. The IMP supplied for this study is

investigational and under no circumstances may be used for purposes other than those described in this protocol.

The Investigator agrees not to supply the IMP to any person other than the patients participating in the study. IMP may not be relabeled or reassigned for use by other patients except under special circumstances previously approved by Atox Bio.

The Investigator will retain and store all original vials until these vials are inventoried by the unblinded study site monitor. Unless otherwise instructed by the Atox Bio medical monitor, the Investigator agrees to destroy (per the site's drug destruction policy) all original vials at the end of the study, whether empty or containing IMP, to Atox Bio or designee. The Investigator agrees neither to dispense the IMP from, nor store it at any site other than the study sites agreed upon.

A separate unblinded study monitor will ensure proper disposition of original vials whether empty or full of IMP. Appropriate IMP disposition documentation will be maintained as part of the source documentation.

### 8.1.5 Disallowed Medications

Study participants should not receive immunosuppressant agents or chemotherapy and should not be given high doses of steroids (defined as >40 mg or 0.50 mg/kg prednisone (or steroid with equivalent activity)/day for ≥2 weeks (see Appendix G – Section 18.7).

NOTE: Adrenal replacement therapy (corticosteroids) is permitted in patients with septic shock at the discretion of the Investigator balancing the potential benefits and risks in this situation. The optimal treatment regimen in this setting is not resolved. Investigators are referred to current Surviving Sepsis Campaign guidelines (www.survivingsepsis.org) as a reasonable source of guidance for steroid replacement therapy in septic shock patients.

Use of agents that can cause significant nephrotoxicity (e.g. non-steroidal anti-inflammatory drugs (NSAIDS), aminoglycosides, colistin, amphotericin B) should be avoided where possible. A list of potentially nephrotoxic medications is provided in the Study Procedure Manual.

### 8.1.6 Allowed Medications

#### 8.1.6.1 Antimicrobial Agents

All patients will receive one or more antimicrobial drugs used as SoC to treat the primary or subsequent infections. Antimicrobial agents include antibacterial, anti-fungal, anti-viral and anti-parasitic drugs. Topically applied antimicrobial agents should be included. Any other medications whether drugs or biologics used to treat the patient should be identified as non-antimicrobial medications.

Each antimicrobial agent will be identified by its generic or trade name and reported in the eCRF. Information should include the dose, dosing frequency, route of administration, duration (start and stop times and dates), and reason for administration (to treat primary or secondary infection or for surgical prophylaxis).

#### 8.1.6.2 Non-antimicrobial Medications

Contrast-enhancing agents used to evaluate patients for abdominal infection (or other complications following study entry) are allowed but should be captured as described below for other non-antimicrobial drugs.

Non-antimicrobial (ancillary) drugs administered from the time of patient screening until end of study will be recorded in the eCRF. Information to be collected should include generic or trade name, route of administration, duration (start and stop dates) and reason for administration. A list of medications that are not required to be captured in the ancillary medication eCRF is provided in the Study Procedure Manual.

## 8.2 Study Medication Compliance

Compliance will be monitored by recording the total volume of each investigational agent actually delivered to each study patient.

## 8.3 Precautions and Overdose

### 8.3.1 Study Drug - Reltecimod

#### 8.3.1.1 Precautions

Currently available safety information does not require any special precautions to be exercised during treatment with Reltecimod. Analysis of safety data collected in Reltecimod Phase 1 and 2 studies, did not reveal AEs that were determined as related to Reltecimod (including possibly, probably and definitely related to study drug). In animal toxicology studies no target organs were identified.

#### 8.3.1.2 Over Dosage

To date, throughout the Reltecimod clinical development program, a single patient (study ATB-201) received an accidental overdose of approximately 30% (received 0.67 mg/kg instead of 0.50 mg/kg). This patient had no AEs determined as related to study drug. He had an SAE of acute renal failure that is expected in NSTI patients and was related to the patient's underlying NSTI. All the patient's AEs were resolved. In case of an overdose (defined as a 100% increase over the 0.50 mg/kg intended dose of Reltecimod), the site staff should contact the medical monitor. Additionally, the patient should be monitored and followed-up according to the best medical practice.

### 8.3.2 Placebo Comparator

No known or expected adverse reactions are associated with pyrogen-free, preservative-free, physiologic saline.

#### 8.3.2.1 Precautions

None for placebo comparator.

# 9. STUDY PROCEDURES

## 9.1 Informed Consent

The ICF is in compliance with ICH GCP Guidelines, and in accordance with the Federal Regulations as detailed in 21 CFR §50.25 and the Declaration of Helsinki.

Prior to entering the study, the Investigator/designee will explain the nature of the study to each patient or LAR its purpose, expected duration, alternative forms of therapy available and the benefits and risks of study participation. After this explanation and before entering the study, the patient or LAR will read and understand the ICF and voluntarily sign a consent form in the presence of the Investigator/designee. LAR may utilize phone/fax/email/e-consent or written consent as allowed by the local institutional policies and procedures.

The patient will be given a copy of the signed/dated ICF.

## 9.2 Clinical and Laboratory Procedures

### 9.2.1 Start of Drug Administration Clock

The IV drug administration clock of maximal 6 hours starts once the patient is diagnosed with Stage 2 or 3 AKI as established at the study site, only after the decision is made by the attending surgeon at the study site for a surgical or interventional radiology procedure for the abdominal infection or after confirmed diagnosis of abdominal infection has been established by a surgical or interventional radiology procedure; or after surgical confirmation of NSTI as described in the inclusion criteria (Section 76.1).

### 9.2.2 Inclusion/Exclusion Criteria

The inclusion and exclusion criteria are specified in Sections 6.1 and 6.2. These criteria determine patient eligibility for recruitment. All patients must be evaluated for the presence of all inclusion criteria and the absence of all exclusion criteria before they are eligible to receive study drug.

### 9.2.3 Medical and Surgical History

A complete medical history identifying clinically relevant past medical and surgical conditions and active medical or surgical conditions will be reported on the Medical History eCRF. All chronic medications will be identified and characterized by trade or generic name, route of administration as well as reason for use from 14 days prior to study drug administration to Day 28.

Baseline signs and symptoms, defined as pre-emergent adverse events, should be captured on the Baseline Signs and Symptoms eCRF form.

### 9.2.4 Physical Examinations

Physical examination will include a clinically appropriate examination of vital organ systems. These should include at minimum cardiovascular, respiratory, abdomen, extremities, and neurologic body systems. Physical exams do not need to be performed if subject is being evaluated by a visiting nursing service as an outpatient.

#### 9.2.4.1 Interim Physical Examinations (Symptom-driven)

Interim PE will be targeted to include clinically appropriate examination of specific organ systems based on patient related signs and symptoms.

### 9.2.5 Concomitant Medications

All concomitant medications, antimicrobial & non-antimicrobial, (with the exception of over the counter medications (unless nephrotoxic), vitamins, laxatives, intravenous fluid and electrolyte replacement, parenteral nutrition, topical medications and other selected medications as described in the Study Procedure Manual) will be entered into the eCRF and identified by their generic or trade name.

Information about antimicrobial medications, immunosuppressants, and nephrotoxic drugs should include the dose, dosing frequency, route of administration, duration (start and stop times and dates), and reason for administration (to treat primary or secondary infection or for surgical prophylaxis).

Information to be collected about non-antimicrobial medications, immunosuppressants, or nephrotoxic drugs should include generic or trade name, route of administration, duration (start and stop dates) and reason for administration.

Timing and adequacy of antibiotic therapy (based on institutional guidelines, baseline pathogens and antimicrobial sensitivity) will be reviewed by the Principle Investigator.

### 9.2.6 Abdominal Infection Type

The cause and type of the abdominal process (e.g. complicated appendicitis or diverticulitis, peritonitis due to perforation of small or large intestine, post-traumatic peritonitis) causing peritonitis and abdominal infection along with factors predisposing to abdominal infection will be captured. The date and time of diagnosis of abdominal infection and type of surgical or interventional procedure(s) to establish source control through Day 14 will be recorded.

### 9.2.7 NSTI Infection Site

Details of the NSTI will be recorded on the eCRF and include: “clinical characteristics” (as a specific subset of NSTI) at the time of enrollment; location of primary infection; extension of infection; date of onset of symptoms, identified predisposing factors (trauma, surgery, IV drug use, comorbidities such as diabetes or obesity, bites; prior surgical procedures related to the etiology of NSTI; prior surgical procedures for the treatment of the primary infection site and whether those procedures were considered adequate; antimicrobial use from the date of onset of current illness (may predate diagnosis of NSTI); description of the NSTI lesion; date and time of surgical intervention for NSTI and surface area of NSTI debridement (when available).

The primary NSTI infection site will be described in detail. Any visible wound or drainage will be characterized as to amount, and cellular composition (purulent, sero-sanguineous, sanguineous, other). Tissue edema, focal pain and presence of subcutaneous crepitus, the presence of tissue discoloration, blisters, bullae or necrosis will be identified. The extent of progression of necrosis as well as the need for repeated surgical procedures will be documented by the Investigator.

### 9.2.8 Acute Kidney Injury

During screening, it will be recorded whether the patient presented with Stage 2 or 3 AKI, or developed Stage 2 or 3 AKI within 48 hours after the suspected or confirmed diagnosis of abdominal infection, or surgical confirmation of NSTI. If a reference (baseline) serum creatinine value(s) is/are available from the past 12 months, the reference serum creatinine value(s) and date(s) obtained will be entered. If the subject does not have a reference serum creatinine value, it will be noted if the serum creatinine is ≥2.0 fold normal for age, race, and gender, and the length of the largest kidney by CT or renal ultrasound.

The stage of AKI (Stage 2 or 3) and how AKI was diagnosed (serum creatinine or urine output or both) will be recorded. The screening creatinine value prior to study drug administration as well as additional creatinine values from presentation or around (before) time of diagnosis of abdominal infection or NSTI should be entered. Urine output should be computed from presentation or around (before) time of diagnosis of abdominal infection or NSTI after accurate urine output is recorded. After study drug administration, urine output is collected while subject is in the ICU or step-down unit (or equivalent) with or without a Foley catheter in place through Day 7.

If receiving RRT, then the type of RRT and net fluid removed per RRT session will be collected through Day 28. Additional renal imaging or renal procedures (e.g., renal biopsy) performed as part of SoC through Day 28 will be entered in the eCRF.

### 9.2.9 Vital Signs

Vital signs include heart rate, systolic and diastolic blood pressure, respiratory rate (spontaneous, assisted or controlled) and temperature. While these may be determined many times during the course of the patient's hospitalization, recording vital signs (to be taken during the morning tests) in the eCRF will be based on once daily readings for specified time sequences according to time and events, Section 18.1.

### 9.2.10 Clinical Scores

Clinical scores/criteria components will be collected in the study. APACHE II score criteria will be determined only at screening (see Section 18.2) while SOFA score will be determined throughout the study (see Section 18.3). APACHE II will be used to determine disease severity while SOFA score will be evaluated as an inclusion criteria and as a secondary clinical endpoint. Individual parameters of the SOFA score will be collected and will also be correlated to response. All scores, except the Screening SOFA, will be calculated retrospectively. Data will be recorded in the eCRF at specified time points according to time and events, see Section 18.1.

#### 9.2.10.1 SOFA Score Definition

Screening SOFA

Includes measurements of 6 organ systems (cardiovascular, respiratory, renal, coagulation, GI/hepatic, CNS). Screening SOFA score should be evaluated any time after arrival at study site hospital and within 6 hours prior to study drug administration.

SOFA Score

Measurements of 6 organ systems, including CNS. To be measured on Days 1, 3, 7, and 14, and calculated retrospectively.

SOFA Respiratory Parameter

In case it is not possible to take arterial blood gases to determine the SOFA respiratory parameter, SpO2/FiO2 ratio can be imputed for PaO2/FiO2 ratio.

### 9.2.11 Clinical Laboratory Assessments

Safety laboratory investigations will include hematology (CBC including platelets and white cell differential), chemistry (Glucose; Electrolytes (Sodium, Potassium, Chloride, Bicarbonate); renal function tests (Urea/BUN, Serum Creatinine); liver function tests (Albumin, Bilirubin Total, Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP); Total Protein); Calcium; Phosphorus.

CRP (standard test, not high sensitivity-hsCRP) to evaluate inflammatory response will be obtained at Screening and at Days 7, 14 and 29. Spot urine (preferably from first morning void) will be obtained for albumin to creatinine ratio.

Pregnancy testing will be done on all women of childbearing potential participating in the study (using blood test or urine test whichever is faster; blood test only in France).

Clinical laboratory assessments will be collected at intervals according to time and events in Section 18.1.

#### 9.2.11.1 Immunogenicity

Blood (6 mL) for serum will be collected at screening, Days 14, 29 and 90 visits for immunogenicity testing. The specific assay to test for immunogenicity against Reltecimod will be determined at the end of the trial. The study blood samples will be processed then aliquoted into three cryovials, flash frozen, stored in -70ºC freezer prior to transport to the Central Lab. The study sites shall send all blood (serum) samples collected under this protocol to the Central Lab (see Laboratory Manual). The results of any analyses of the samples will be blinded to the study staff during the study and will not impact the medical management of the patient.

#### 9.2.11.2 AKI Biomarker – Optional Sub-study

Urine (5 mL) and blood (5 mL) for plasma will be collected for evaluations of biomarkers to assess AKI as an optional sub-study. The specific AKI biomarkers will be determined at the end of the trial, dependent of the effects of the intervention on the renal endpoints. Numerous novel candidate protein AKI biomarker targets may be analyzed by immunoassay in the samples from the preliminary studies. Analyzed biomarkers may include novel targets not previously described in the literature as well as existing biomarkers, which will be measured for comparison.

The study blood and urine samples will be processed, flash frozen, stored in -70º C freezer prior to analysis. The results of any analyses of the samples will be blinded to the study staff during the study and will not impact the medical management of the patient. The study

sites shall send all blood (plasma) and urine samples collected under this protocol to the Central Lab (see Laboratory Manual). The samples may be stored up to 5 years but will be used by the Investigators only to identify and validate biomarker targets for assessment of at-risk patients and will not be used for any other purpose. Samples will be stored at the Central Lab. Any excess sample will not be destroyed but will be maintained for additional study as described above. Each sample will not be individually identifiable.

#### 9.2.11.3 Systemic Inflammatory Biomarkers – Optional Sub-study

The whole blood leukocyte transcriptome (RNA expression) profile testing and evaluation of systemic inflammatory biomarkers is an optional sub-study of the main protocol.

The purpose of the leukocyte transcriptome (RNA Expression Profile) is to obtain insight in the effect of Reltecimod on the host response to SA-AKI by detailed and unbiased analysis of the blood leukocyte response. For this, 5 mL of whole blood will be collected at each time point. Systemic inflammatory biomarkers will include serum cytokines or chemokines such as (but not limited to): IL-6, IL-8, INF-γ, TNF-α, IL-17A, IL-3 and RANTES. For this, 10 mL of whole blood will be collected at each time point.

Blood will be collected before initiation of Reltecimod administration and at 4-6 hours, 24±4 hours, 48±4 hours, and 72±4 hours post study drug administration. At each of these time points whole blood leukocyte counts and differentials will be determined by the local laboratory. Samples may be stored for up to 5 years but will only be used for the evaluation of the effect of Reltecimod on host response to SA-AKI. Results will not be reported to the treating physician or the subjects (or their relatives).

All patients that have at least 3 systemic biomarkers samples taken: one before study drug administration, and at two additional time points post dosing will be included in the systemic biomarker analysis.

#### 9.2.11.4 Total Blood Volume Collected

The total maximal volume of blood to be collected in the study is composed of study specific tests as well as tests that are part of the SoC. The list below represents the combined blood quantities. Approximately 9 tablespoons (125 mL) of blood will be collected from each patient with an additional 6 tablespoons (90 mL) of blood collected if the patient also participates in the both optional biomarker sub-studies.

**Table 5: Maximal blood draw by visit**

| Visit | Type | Maximal Volume (cc) |
|---|---|---|
| 1<br>SCR | CRP | 3 |
| | Chemistry | 4 |
| | Hematology | 4 |
| | Arterial Blood Gas* | 2 |
| | Pregnancy test | 2 |
| | Blood Culture | 20 |
| | Immunogenicity sample | 6 |
| | AKI Biomarker | 5 |

| Visit | Type | Maximal Volume (cc) |
|---|---|---|
| | Systemic Inflammatory Biomarkers - blood leukocyte transcriptome profile and cytokines / chemokines | 15 |
| | **Total Volume** | **61** |
| 2<br>Day 1 | Arterial Blood Gas* | 2 |
| | Chemistry *(only Creatinine and Bilirubin)* | 3 |
| | Hematology | 4 |
| | Systemic Inflammatory Biomarkers - blood leukocyte transcriptome profile and cytokines / chemokines | 15 |
| | **Total Volume** | **24** |
| 3<br>Day 2 | AKI biomarker | 5 |
| | Chemistry (*only Creatinine*) | 3 |
| | Systemic Inflammatory Biomarkers - blood leukocyte transcriptome profile and cytokines / chemokines | 15 |
| | **Total Volume** | **23** |
| 4<br>Day 3 | Chemistry (*only Creatinine and Bilirubin*) | 3 |
| | Hematology | 4 |
| | Arterial Blood Gas* | 2 |
| | Systemic Inflammatory Biomarkers - blood leukocyte transcriptome profile and cytokines / chemokines | 15 |
| | **Total Volume** | **24** |
| Day 4 | Systemic Inflammatory Biomarkers - blood leukocyte transcriptome profile and cytokines / chemokines | 15 |
| | **Total Volume** | **15** |
| 5<br>Day 7 | CRP | 3 |
| | Chemistry | 4 |
| | Hematology (CBC with differential and platelets) | 4 |
| | Arterial Blood Gas* | 2 |
| | AKI biomarker | 5 |
| | **Total Volume** | **18** |
| 6<br>Day 10 | Chemistry (*only Creatinine)* | 3 |
| | **Total Volume** | **3** |
| 7<br>Day 14 | Arterial Blood Gas* | 2 |
| | CRP | 3 |
| | Chemistry | 4 |
| | Hematology (CBC with differential and platelets) | 4 |
| | Immunogenicity sample | 6 |
| | **Total Volume** | **19** |
| 8<br>Day 21 | Chemistry (*only Creatinine)* | 3 |
| | **Total Volume** | **3** |
| 9<br>Day 29 | Chemistry (*only Creatinine & Albumin*) | 3 |
| | Hematology (CBC with differential and platelets) | 4 |
| | Immunogenicity sample | 6 |
| | CRP | 3 |
| | **Total Volume** | **16** |
| Visit 10<br>3 to 21 Days after Visit 9 | Chemistry *(only Creatinine)* | 3 |
| Visit 11<br>Day 90 | Chemistry (*only Creatinine*) | 3 |
| | Immunogenicity sample | 6 |

| Visit | Type | Maximal Volume (cc) |
|---|---|---|
| | **Total Volume** | **9** |
| **Total Study** | | **215** |

* Obtain arterial blood gases (ABG) if clinically indicated. Otherwise record SpO2 value and also FiO2.

#### 9.2.11.5 Microbiology

Microbiological testing will follow the SoC of treatment of patients with abdominal infection or NSTI. At the time of initial surgical exploration, a sample from the abdominal infection site (peritoneal fluid, abscess fluid, tissue) or NSTI site (tissue) will be cultured by the local microbiology laboratory. Results from blood cultures (if available) drawn at the onset of infection, will retrospectively be registered.

Antibiotics received prior to the primary surgical intervention will be identified as well as antibiotics received during the study evaluation window of Days 1 to 28.

Bacterial isolates obtained from the patients in the study and considered to be pathogens will be identified by genus and species using the methods established in the *Manual of Clinical Microbiology*[40]. Results will be used to categorize patients according to microbiology organism group (Gram-positive, Gram negative, anaerobic, mixed infection).

Susceptibility testing will be performed on all aerobic pathogens according to clinical laboratory standards institute (CLSI) criteria.

Blood culture for both aerobic and anaerobic bacteria will be taken during the screening process if not already obtained previously during evaluation of acute abdominal infection or NSTI presentation. Repeat blood cultures for microbiology will also be obtained according to physician discretion, if the patient is suspected to have a new or progressive infection (if deterioration in the hospitalized patient's condition is observed (e.g. spiking a fever).

#### 9.2.11.6 Renal Replacement Therapy Guidelines

Renal replacement therapy guidelines are provided only to guide the clinicians. Initiation and stopping of renal replacement therapy can occur based on the clinicians/institution's protocols/judgement. Continuous and intermittent-non-continuous modalities such as intermittent hemodialysis (IHD) are allowed after administration of study drug. RRT may be started prior to study drug administration as long as the patient is off the treatment from time of study drug administration and up to at least one hour post study drug administration.

##### 9.2.11.6.1 Initiation of Renal Replacement Therapy

Initiation of RRT is based on the conventional criteria described by Bellomo 2012[44].

Conventional criteria for initiation of RRT in AKI:

1. Anuria (negligible urine output for 6 hours)
2. Severe oliguria (urine output < 200 mL over 12 hours)

3. Hyperkalemia (Potassium concentrations >6.5 mmol/L)
4. Severe metabolic acidosis (pH <7.2 despite normal or low partial pressure of carbon dioxide in arterial blood)
5. Volume overload (especially pulmonary oedema unresponsive to diuretics)
6. Pronounced azotemia (urea concentrations >30 ml/L or creatinine concentrations >300 umol/L)
7. Clinical complications of uremia (e.g., encephalopathy, pericarditis, neuropathy)

#### 9.2.11.6.2 Timing of Stopping Renal Replacement Therapy

Termination of dialysis is based on criteria as used in the VA/NIH Acute Renal Failure Trial Network Study[45]. If (on Continuous Renal Replacement Therapy (CRRT) or between IHD sessions) diuresis >30 mL/hour and there are no other indications for RRT, then the endogenous creatinine clearance (ECC) should be calculated using a 6-hour urine collection period. If ECC >20 mL/min, CRRT should be discontinued. If ECC <12 mL/min, RRT should be continued. If ECC >12 and <19 mL/min, continuation/termination will be the decision of the treating physician. Exact criterion or criteria, corresponding values (e.g. Na+, K+ or pH) and deviations (e.g. RRT not started when indicated or RRT started when not indicated) need to be meticulously recorded in the eCRF.

## 10. EVALUATION MEASURES FOR EFFICACY

Efficacy measures are described in Section 5, “Study Objectives”.

### 10.1 Primary Efficacy Measure

- Rates of achieving the primary endpoint of freedom from durable loss of renal function (defined as alive, free of dialysis, and less than a 37% loss of eGFR (measured with the MDRD formula from the patient’s reference eGFR)) at Day 28.

AKI stage and recovery will be determined by a blinded adjudication committee as described in Section 10.4.

### 10.2 Secondary Efficacy Measures

- Rates of the primary endpoint at Day 14 between the Reltecimod- and placebo-treated patients
- To compare time to the primary endpoint between the Reltecimod- and placebo-treated patients
- AKI-free days over 14 and 28 days
- Resolution of organ dysfunction (organ resolution is defined as having a total SOFA score of ≤1) at Day 14
- Resolution of specific organ dysfunction defined as having an individual organ SOFA score of ≤1 at Day 14
- Critical care and hospital stay parameters
  - Hospital length of stay

  - ICU-free days in 28 days
  - Ventilator days
  - Ventilator free days in 28 days
  - Vasopressor days
  - Vasopressor free days in 28 days
  - RRT free days (days alive and free of RRT) in 28 days
- Patient survival at Days 14 and 28
- Presence of Stages 1, 2 or 3 AKI (using the KDIGO criteria) in patients with abdominal sepsis or NSTI

### 10.3 Exploratory Efficacy Measures

- Rates of improvement in durable loss of renal function (defined as alive, free of dialysis and improvement leading to a lower AKI stage but no better than Stage 1 AKI) at Days 14, 28 and 90
- AKD stages (AKD 0, 1, 2, 3 and 3F) at Days 14 and 28
- Incidence of CKD at Day 90
- Survival at Day 90
- Primary endpoint by baseline pathogen
- Evaluation of RRT use (i.e., type of RRT)
- Plasma and urinary biomarkers in patients with AKI
- To conduct an exploratory evaluation of blood leukocyte transcriptome (RNA expression) profiling in patients with SA-AKI and compare genomic profile in patients treated with Reltecimod versus placebo
- To define potential surrogate biomarkers (systemic) that exhibit change from baseline due to treatment with Reltecimod
- Data (including financially related data) will be gathered to evaluate possible health economic outcomes from the study, including but not limited to:
  - Length of stay (ICU and overall hospital)
  - Number of re-admissions
  - Reduction in ICU admission rates (depending on patient population being selected – i.e. severity of patients
  - Relative reduction in any physical outcome (including in-hospital deaths)
  - Persistent kidney injury

### 10.4 Adjudication Committee for Evaluation of AKI Stage and Recovery

Experts chosen for the AKI Adjudication Committee will be independent of the Sponsor and neither they nor their institutions participated in the sample collection or sample measurement studies.

The procedures for adjudication will be defined in advance of the study by consensus among the three adjudicators and the Principal Investigator in a series of face-to-face and teleconference meetings. Adjudicators collectively will determine which variables would be extracted from the medical record and provided to them for adjudication. These variables will include reference creatine values (as defined in the Inclusion Criteria) and serum

creatinine values up to 90 days after enrollment, all available urine output data prior to dosing and up to 7 days after enrollment when in the ICU or step-down unit, daily fluid balance and use of diuretics. In addition, the date(s) of RRT, death and ICU discharge will be provided, as well as age, sex, race, weight, reason for hospital and ICU or step-down unit admission and medical history. Adjudicators may also request additional information for individual patients.

Each adjudicator will be provided a form for each patient containing all the clinical information described above. Adjudicators will be blinded to group assignment and clinical data will be identified only by anonymized identification number. Adjudicators will indicate their assessment of AKI staging and recovery independently without consultation with each other. The basis for the adjudication will be the KDIGO consensus criteria (based on RIFLE/AKIN definitions for AKI) corresponding to Stages 1to 3 (mild to severe). A two thirds majority was predefined for use as the final adjudication. The forms will be provided to the external statisticians for analysis.

# 11. EVALUATION CRITERIA FOR SAFETY

## 11.1 Safety Measures

Safety measures in this study include AEs, clinical safety laboratory, clinical parameters (HR, BP, vital signs), secondary infections and determination of survival. These are described in more detail in Section 5, “Study Objectives”, and the specific times of these parameters are described under “Study Visits and Procedures” in Section 18, Appendix A.

AEs including SAEs will be assessed throughout to Day 28, and clinical safety laboratory throughout to Day 14. Survival will be determined throughout 90 days.

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, Investigators, and the Sponsor, and is mandated by regulatory agencies worldwide. The Sponsor or its affiliate has established SOP in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information; all clinical studies sponsored by Sponsor or its affiliates will be conducted in accordance with these procedures.

Patients (or their designee, if appropriate) must be provided with information indicating the name of the IMP, the study number, the Investigator's name and a 24-hour emergency contact number, and, if applicable, excluded concomitant medications.

### 11.1.1 Adverse Event Definitions and Classifications

The following definitions of terms are guided by the ICH and the United States Code of Federal Regulations [21 CFR § 312.32].

#### 11.1.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated

with the use of an IMP, whether or not considered related to the IMP. This definition includes illnesses or injuries, and exacerbations of pre-existing conditions.

#### 11.1.1.2 Serious Adverse Event

A SAE is an AE occurring during any study phase (i.e., treatment, follow-up), and at any dose of the IMP or placebo, that fulfils one or more of the following criteria:

- Results in death (for purposes of this trial deaths will be captured as clinical outcomes and only recorded as an SAE if deemed related to IMP)
- Is life-threatening (i.e., the patient was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred)
- Requires or prolongs hospitalization
- Results in persistent or significant disability or incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect
- Is an important and significant medical event (e.g., allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse) that, based upon appropriate medical judgment, may jeopardize the patient and/or may require medical or surgical intervention to prevent one of the other outcomes defining SAE.

#### 11.1.1.3 Adverse Reaction

Any AE for which there is a reasonable possibility that the IMP caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the IMP and the AE.

#### 11.1.1.4 Expectedness of the Adverse Event

Expected AEs are AEs consistent with the applicable product information provided by the Sponsor (the Investigator's Brochure for an investigational product). The Sponsor, in consultation with the medical monitor, determines expectedness. If a SAE is **expected** no further action is required. If the Sponsor and medical monitor determine that SAE is **unexpected,** then the event may meet criteria for expedited SAE notification to the regulatory agencies.

From preclinical data and completed clinical studies to date, there are no expected adverse events for Reltecimod.

### 11.1.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is both unexpected (not consistent with the observed or expected risk information applicable to the IMP) and also meets the definition of "serious" described above. All 3 of the definitions contained in the US Food and Drug Administration (FDA) requirement for expedited reporting must be met to qualify for expedited reporting to FDA: 1) Serious, 2) Unexpected, and 3) Suspected adverse reaction. AEs that do not meet the

requirements for expedited reporting will be reported to FDA in the IND Annual Report. SUSARs that are fatal or life-threatening will be reported to FDA as soon as possible, but no later than 7 calendar days after Sponsor's initial receipt of the information (21 CFR 312.32(c)(2)). Other SUSARs will be reported to FDA within 15 calendar days of initial receipt or after determining that the information qualifies for reporting under 21 CFR 312.32(c)(1).

European sites will comply with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 and E2A reporting requirements or local country regulatory authority requirements.

### 11.1.3 Adverse Events Based on Examinations and Tests

Deterioration as compared to baseline in protocol mandated laboratory values, vital signs and other safety variables should only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IMP. However, the Investigator may record such findings as an AE at his/her discretion in addition to completing an unscheduled laboratory/vital signs page with the information on the clinically significant test abnormality. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a PE, dermal examination or lung auscultation as compared with the baseline assessment will be reported as an AE. Clinically relevant deterioration in unscheduled assessments of laboratory/vital signs/ECG parameters should be reported on additional eCRF pages.

Wherever possible, the reporting Investigator uses the higher level medical concept, rather than the laboratory term (e.g., anemia versus low hemoglobin value).

### 11.1.4 Pregnancies

If pregnancy is detected after the administration of study drug through Day 90, the patient will be followed-up until resolution. The Investigator must immediately record the pregnancy on the pregnancy reporting form and notify Sponsor/designee Pharmacovigilance by telephone and fax form within 24 hours of becoming aware of the event. In addition, the Investigator must report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. If pregnancy is reported in a female partner of a male patient, the female partner will be asked to sign a separate consent form to allow the site personnel to capture data about the pregnancy and to follow the pregnancy until completion. No information about such pregnancies will be captured without informed consent from the female partner.

### 11.1.5 Relationship to Investigational Medicinal Product

The relationship of an AE to the administration of IMP (unrelated, probable or definite) is a clinical decision based on all available information at the time of the completion of the eCRF.

IMP relationship will be evaluated according to the following definitions:

**Unrelated**: includes the existence of a clear alternative explanation (e.g., mechanical bleeding at surgical site) or non-plausibility (e.g., the patient is struck by an automobile, at least where there is no indication that the IMP caused disorientation that may have led to the event; cancer developing a few days after IMP administration).

**Probable**: The AE, including clinical laboratory abnormality, follows a reasonable sequence from the time of IMP administration, follows a known response pattern of the IMP class, is unlikely to be attributed to the patient's clinical state, and is confirmed by improvement on stopping the IMP (de-challenge).

**Definite**: The AE, including clinical laboratory abnormality, follows a plausible sequence from the time of IMP (or placebo) administration; follows a known or expected response pattern to the IMP class; cannot be explained by disease or it disappears or decreases on cessation or reduction in IMP dose; and/or it reappears or worsens when the IMP is re-administered.

### 11.1.6 Severity

The Investigator will determine the intensity of each AE using the following terms and definitions:

**Mild**: An AE that was usually transient required no intervention or special treatment and did not interfere with usual/normal activities.

**Moderate**: An AE that interfered with usual/normal activities but was ameliorated by therapeutic measures.

**Severe**: An AE that was intense or debilitating and which interfered with usual/normal activities. Recovery was usually aided by therapeutic measures. Discontinuation of IMP might have been required.

## 11.2 Reporting of Adverse Events

All AEs that occur between randomization through Day 28 visit will be reported. AEs that start prior to study drug administration will also be captured. Worsening signs and symptoms of the underlying disease will be reported as AEs.

The course of each event should be followed until resolution. All unresolved AEs should be followed-up by the Investigator until the events are resolved, or the AE is stabilized and otherwise explained.

AEs should be recorded according to findings and abnormalities detected by the Investigator. Specific capturing of potential secondary infections will take place. In addition, patients should report AEs voluntarily and in response to general, non-directed questioning. For each AE reported by the patient, or observed by the Investigator, the Investigator should obtain all the information required to complete the AE page of the eCRF, in accordance with the guidelines that accompany it.

Atox Bio or designee assumes responsibility for appropriate reporting of SAEs to the regulatory authorities. Atox Bio or designee will also report to the Investigators all SAEs that are unexpected and associated with the use of the drug.

The Investigator must report these events to the appropriate IRB/IEC in accordance with local regulations.

## 11.3 Reporting of Serious Adverse Events

All SAEs occurring with any patient participating in this clinical study must be recorded. All deaths and SAEs must be reported within 24 hours of becoming aware of the event to the Sponsor or designee. All SAEs beginning within 28 calendar days after the last exposure to IMP must be recorded.

### 11.3.1 Initial Report

Once an Investigator becomes aware that a SAE has occurred in a study subject, the Investigator (or designate) must complete the information in the SAE eCRF pages WITHIN 24 HOURS. The SAE eCRF pages will always be completed as thoroughly as possible with all available details of the event. Even if the Investigator does not have all information regarding a SAE, the SAE eCRF pages should still be completed within 24 hours. The report should contain, at a minimum, the following information:

- Subject identifiers (i.e., subject number)
- Suspected medicinal product (or if related to IMP, note "Reltecimod/Placebo")
- Adverse event term (must be listed as serious)
- Contact information for person reporting event

Once additional relevant information is received, the SAE eCRF pages should be updated WITHIN 24 HOURS.

The medical monitor is available on a 24-hour basis if clinical personnel wish to discuss any safety related events.

#### 11.3.1.1 Electronic SAE Reporting System Back-up

If the electronic SAE reporting system does not work, the Investigator (or designate) must complete, then date and sign a SAE Report Form. The site should scan the document and email it to the medical monitor at davidw@atoxbio.com and wayned@atoxbio.com within 24 hours.

This back-up system should only be used if the electronic SAE reporting system is not working and NOT if the system is slow. As soon as the electronic SAE reporting system is working again, the Investigator (or designate) must complete the SAE eCRF pages within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

### 11.3.2 Follow-up and Final Reports

After the initial AE/SAE report, the Investigator is required to proactively follow each subject and provide further information on the subject's condition to Atox Bio.

All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until study end.

Follow-up information to an initial SAE report should be reported in the SAE eCRF pages within 3 business days. At the time of resolution of a SAE, a final report must be provided to the Sponsor by completing the appropriate SAE Report Form.

Any AE, regardless of severity, and whether or not ascribed to the IMP administration, will be recorded as such using medical terminology in the source documentation and on the appropriate eCRF pages. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. nausea and vomiting should be reported as "gastroenteritis" if gastroenteritis is the etiology of both). However, worsening sign(s) and symptom(s) of a diagnosis should be recorded separately. Patients withdrawn from the study due to AEs will be followed by the Investigator until the outcome is determined and, when appropriate, additional written reports and documentation will be provided.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed-up until either:

- the event resolves
- the event stabilizes
- the event returns to baseline, if a baseline value is available
- the event can be attributed to agents other than the study drug, or
- the event can be attributed to factors unrelated to study conduct

## 11.4 Disease Related Adverse Events

It is recognized that the patient population with abdominal sepsis or NSTI who require critical care support will experience a number of common aberrations in laboratory values, signs, and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an AE unless they require significant intervention, lead to discontinuation of blinded study medication, felt to be related to blinded study medication or are considered to be of concern, in the Investigator’s clinical judgment. Examples of the type of AEs that may be associated with the abdominal infection, NSTI and sepsis are listed below.

### 11.4.1 List of Adverse Events that may be Associated with Abdominal Infection, NSTI, and Sepsis

Acute respiratory failure; respiratory distress; acute lung injury; acute respiratory distress syndrome (ARDS); acute renal failure; coagulation dysfunction; decreased platelets count; neutropenia; hypothermia; fever, bacteremia; sepsis, septic shock; hypotension; metabolic acidosis, pleural effusion; abdominal compartment syndrome; repeated surgeries/debridement; amputation.

For purposes of this study, deaths will be captured as clinical outcomes and do not need to be reported as SAEs unless felt related to study drug administration.

### 11.5 Safety Monitoring

The study medical monitor will assess all SAEs on an ongoing basis. Attention will be given to SAEs assessed as drug-related. The medical monitor may request unblinding of the treatment allocation of a patient for regulatory reporting purposes. The medical monitor will convene the independent data monitoring committee (iDMC) on ad-hoc basis if safety concerns arise from the medical monitor review.

### 11.6 Independent Data Monitoring Committee (iDMC)

An iDMC will be established to evaluate the safety of the study. An iDMC review of the safety data is planned after 60 patients (and possibly a second review depending on sample size re-estimation) have completed 28 days of the study.

For each planned iDMC review, all safety data on all patients who received one dose of Reltecimod will be made available to the iDMC. The data reviewed by the iDMC will be unblinded and presented by group to facilitate recommendations to the Sponsor. Data submitted to the iDMC review may be unaudited. A designated unblinded statistician will provide unblinded safety data to the iDMC using programs constructed and validated by the blinded Study Statistician and Statistical Programming Team. Further details on data management will be provided in the statistical analysis plan (SAP).

The iDMC may also meet on an ad-hoc basis when immediate safety concerns arise. In case of urgency, the chair of the committee could address any questions or concerns regarding the safety of the patients.

## 12. STATISTICS

### 12.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study is:

- Rates of achieving the primary endpoint of freedom from durable loss of renal function (defined as alive, free of dialysis, and less than a 37% loss of eGFR; (measured with the MDRD formula from the patient's reference eGFR)) at Day 28.

### 12.2 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints for this study:

- Rates of the primary endpoint at Day 14 between the Reltecimod- and placebo-treated patients.
- To compare time to the primary endpoint between the Reltecimod- and placebo-treated patients over 14 days
- AKI-free days over 28 days
- Time to the primary endpoint
- Resolution of organ dysfunction (organ resolution is defined as having a total SOFA score of ≤1) at Day 14

- Resolution of specific organ dysfunction defined as having an individual organ SOFA score of ≤1 at Day 14
- Critical care and hospital stay parameters
  - Hospital length of stay
  - ICU length of stay
  - ICU-free days in 28 days
  - Ventilator days
  - Ventilator free days in 28 days
  - Vasopressor days
  - Vasopressor free days in 28 days
  - RRT free days (days alive and free of RRT) in 28 days
- Patient survival at Days 14 and 28
- Presence of Stages 1, 2 or 3 AKI (using the KDIGO criteria) in patients with abdominal sepsis or NSTI

### 12.3 Exploratory Measures

- Rates of improvement in durable loss of renal function (defined as alive, free of dialysis and improvement leading to a lower AKI stage but no better than Stage 1 AKI) at Days 14, 28 and 90
- AKD stages (AKD 0, 1, 2, 3 and 3F) at Days 14 and 28
- Incidence of CKD at Day 90
- Survival at Day 90
- Primary endpoint by baseline pathogen
- Evaluation of RRT use (i.e., type of RRT)
- Plasma and urinary biomarkers in patients with AKI
- To conduct an exploratory evaluation of blood leukocyte transcriptome (RNA expression) profiling in patients with SA-AKI and compare genomic profile in patients treated with Reltecimod versus placebo
- To define potential surrogate biomarkers (systemic) that exhibit change from baseline due to treatment with Reltecimod

### 12.4 Safety Endpoints

The following will be evaluated as safety endpoints: AEs, clinical parameters (HR, BP, vital signs), laboratory parameters (clinical chemistry and hematology) and survival.

### 12.5 Synopsis of Key Statistical Approaches

#### 12.5.1 Primary Efficacy Comparison

The primary efficacy comparison involves testing the following one-sided superiority hypotheses: **Ho:** $\pi_{0.50} - \pi_{placebo} \leq 0$ **vs Ha:** $\pi_{0.50} - \pi_{placebo} > 0$; where $\pi_{0.50}$ and $\pi_{placebo}$ represent the true probability of freedom from durable loss of kidney function (alive, free of dialysis, and less than a 37% loss of eGFR (measured with the MDRD formula from the patient's reference eGFR)) at Day 28. Each probability represents the proportion of subjects on each arm expected to achieve freedom from durable loss of renal function. These

hypotheses will be tested using an unadjusted chi-square test at a one-sided type 1 error rate of $\alpha$=0.025. The null hypothesis will only be rejected if the proportion of responders is larger in the active drug group compared to placebo. It is a noteworthy advantage of the sample size re-estimation approach to be used (see details below) that the conventional test statistic may be used to test the primary hypothesis and there is no need to weight subjects randomized after the sample size re-estimation differently from those randomized before the sample size re-estimation.

### 12.5.2 Sample Size Justification

This trial will enroll 120 subjects who will be randomized in a ratio of 1:1 to either Reltecimod 0.50 mg/kg or placebo, each in addition to SoC. Sample size analysis was performed assuming that all patients will be evaluable for the primary endpoint using last observation carried forward (LOCF) for patients missing creatinine on Day 28. The primary efficacy hypothesis will be tested using an unadjusted $\chi^2$ statistic with a one-sided $\alpha$=0.025 significance level. Rejection the null hypothesis will only occur if investigational drug superiority is demonstrated. Statistical power was computed for a range of expected treatment group differences supported by the results of preliminary studies. Table 6 summarizes the statistical power for a fixed sample design with a total sample size of N=120 (60 per group) for various assumptions regarding the success rate in the investigational arm and assuming a success probability of 0.50 among controls. This sample size results in 81.6% power if the true success rates are 75% and 50% for the investigational and placebo, respectively, a group difference of 25%.

### 12.5.3 Sample Size Re-Estimation

A "Promising Zone" sample size re-estimation (SSR) interim analysis (IA) is planned for when between 50% and 67% of the initial sample size is evaluable for the primary efficacy endpoint (Mehta and Pocock 2011)[53]. The purpose of the SSR is to maintain (conditional) power when the treatment group difference is smaller than 0.25, but still clinically meaningful.

A pre-specified maximum sample size expansion will be specified prior to providing unblinded results to the iDMC but in no case will the sample size expansion exceed an additional 200 subjects. With this restriction, only clinically meaningful treatment effects are detectable with good statistical power at the maximum sample size. The specific rules for determining if sample size expansion is permittable and if so, by how much, will ensure control of type 1 error.

Specifically, the sample size will be increased up to the maximum to maintain conditional power to as close to 80% as possible, but only if conditional power at the interim analysis is above a pre-specified threshold that results in control of type 1 error to the desired nominal value. If conditional power falls within the Promising Zone, increasing the sample size up to the pre-specified maximum is at the discretion of the Sponsor.

The pre-specified conditional power threshold is the lower bound of the Promising Zone and its value may be obtained from Table 1 in Mehta and Pocock 2011. It depends on the ratio of the maximum sample size to the initial sample size (1.5, 2, 3, or infinite), the

fraction of the initially planned sample size included in the IA for SSR (0.25, 0.5, or 0.75), and the level of conditional power to be maintained (80% or 90%). Additional scenarios can be determined using linear interpolation. For 80% power, the lower bounds of the Promising Zone range from 0.30 to 0.42 depending on these three parameters. If conditional power falls within the Promising Zone, increasing the sample size up to the pre-specified maximum up to the discretion of the Sponsor.

Table 6 provides a simple evaluation of how the size of maximum sample expansion relates to statistical power for detecting various clinical effect sizes. Table 6 compares statistical power for fixed sample designs with total sample sizes of 120 (the initially planned sample size), 180 (allowing up to 60 more subjects), and 320 (allowing up to 200 more subjects). The selected maximum will be no larger than 200 additional subjects. As noted above, a fixed sample size design randomizing 120 subjects achieves 81.6% power if the treatment group difference is 25% (i.e., 75% versus 50%). Similarly, a fixed sample size design with 180 subjects achieves 82.7% power if the treatment group difference is 21% (i.e., 71% versus 50%). Finally, a fixed sample size design with 320 subjects achieves 82.9% power if the treatment group difference is 16% (i.e., 66% versus 50%). A 16% treatment group difference is still considered clinically meaningful. Therefore, even if a maximum increase of 200 is selected, the study will only have large statistical power to detect clinically meaningful treatment effects.

Additionally, the lower bounds of the Promising Zone when the IA for SSR is performed with 67% of the initially planned sample size is 0.39 when the maximum increase is 60 subjects; but is reduced to 0.31 when the maximum increase is set to 200. If the observed proportions of responders are 0.66 (0.65) and 0.50 for active and placebo subjects, respectively, conditional power will be 0.3905 (0.3148). Therefore, in any case, the observed treatment group differences will need to larger than about 0.15 depending on the scenario, for any sample size expansion to be even allowed under the Promising Zone approach. This makes it unlikely that the treatment group difference will be found to be statistically significant unless the true treatment effect exceeds about 0.15.

**Table 6: Examples of power for fixed sample design (1-sided α=0.025)**

| Control | Reltecimod | Power (N=120) | Power (N=180) | Power (N=320) |
|---|---|---|---|---|
| 0.5 | 0.60 | 0.194 | 0.269 | 0.435 |
| 0.5 | 0.61 | 0.226 | 0.316 | 0.508 |
| 0.5 | 0.62 | 0.261 | 0.367 | 0.581 |
| 0.5 | 0.63 | 0.299 | 0.420 | 0.651 |
| 0.5 | 0.64 | 0.339 | 0.475 | 0.717 |
| 0.5 | 0.65 | 0.382 | 0.530 | 0.777 |
| 0.5 | 0.66 | 0.426 | 0.586 | **0.829** |
| 0.5 | 0.67 | 0.472 | 0.641 | 0.874 |
| 0.5 | 0.68 | 0.518 | 0.693 | 0.909 |
| 0.5 | 0.69 | 0.565 | 0.742 | 0.937 |
| 0.5 | 0.70 | 0.611 | 0.787 | 0.958 |
| 0.5 | 0.71 | 0.656 | **0.827** | 0.973 |
| 0.5 | 0.72 | 0.700 | 0.863 | 0.983 |
| 0.5 | 0.73 | 0.741 | 0.894 | 0.990 |
| 0.5 | 0.74 | 0.780 | 0.919 | 0.994 |
| 0.5 | 0.75 | **0.816** | 0.940 | 0.997 |

### 12.5.4 Futility Analysis

In addition to sample size re-estimation, a non-binding futility analysis will be conducted at the time of the interim analysis. If conditional power is below a pre-specified futility threshold, enrollment may be immediately stopped at the discretion of the Sponsor. The pre-specified threshold will be determined prior to unblinding the data for the interim analysis.

### 12.5.5 Control of Blinding and iDMC

This study will remain blinded as to treatment allocation. The actual randomized treatment allocations will be kept by a contracted third-party responsible only for managing the randomization process. A variable indicating the blinded treatment allocations will not be part of the clinical study data to be managed by the data management contract research organization (CRO). Therefore, only blinded study data will be available to the primary study statistician and responsible primary programming staff.

An iDMC will be utilized in this study. A detailed iDMC charter will be provided to clarify all relevant issues relating to fire-walls to protect against potential operational biases. The charter will provide decision rules, composition of the iDMC members and their conflict of interest statements. A separate unblinded interim analysis statistician will work with the

iDMC to provide unblinded data as necessary for iDMC deliberations. The unblinded statistician will determine the interim analysis conditional power and summarize the implications to members of the iDMC. The iDMC will inform specifically designated individuals from the Sponsor whether conditional power is below the futility zone, above the futility zone but below the Promising Zone, within the Promising Zone, or above the Promising. If within the Promising Zone, the iDMC will be informed as to the increase in sample size required to maintain conditional power to at least 80%, or if this is not possible, that the maximum allowed increase in sample size may be enrolled. The iDMC will then inform specifically designated Sponsor representatives of their recommendations based on the *a priori* plan.

## 12.6 Summary of Other Elements of Analysis Plan

### 12.6.1 Randomization

120 patients will be recruited into the study and randomized to either 0.50 mg/kg Reltecimod or placebo in a 1:1 ratio. Randomization will be performed within site and according to two stratification variables:

- **Acuity of AKI:** whether or not AKI is diagnosed at time of presentation of abdominal infection or surgically confirmed NSTI; or during the 48 hours the suspected diagnosis of abdominal infection or surgical confirmation of NSTI.
- **Subject Age:** ≥18 to ≤75 or >75 to ≤85 years old.

Four computer generated, blocked randomization lists will be provided for each site, one for each of four strata defined on the basis of the 2 by 2 cross-tabulation of the two stratification variables. Within each block, half of the assignments will be to active drug and half to placebo, in random order. Block sizes will be varied.

### 12.6.2 Patient Populations

The following analysis sets are defined:

- Intent-to-treat (**ITT**): The ITT analysis set will include all randomized patients.
- As-Treated (**AT**): The AT analysis set will include all randomized patients who were exposed to study medication (active or placebo). The AT analysis set will be used in primary safety analyses with patients assigned to actual treatment received.
- Modified Intent-to-treat (**mITT**): The mITT analysis set will include patients who were exposed to study medication and who had a definitive diagnosis of abdominal sepsis or NSTI with patients assigned to their intended randomized assignment. The mITT analysis set will be used in primary effectiveness comparisons.
- Per Protocol (**PP**): Optionally, a PP analysis set may be used in secondary effectiveness analyses. The PP analysis would include patients in the mITT analysis set assigned according to actual treatment received and excluding patients with either 1) significant violations of inclusion or exclusion criteria

with potential to confound estimates of drug effects or 2) post randomization protocol violations or intercurrent events with potential to confound estimates of treatment effects. Exclusions from the PP analysis set will be determined based on blinded clinical data. The PP analysis may be further restricted to include patients that survive at 3 least days when evaluating critical care variables.

### 12.6.3 Preliminary and Descriptive Analyses

Before proceeding with between-group comparisons of primary and secondary clinical endpoints, data quality will be assessed by descriptive summaries and graphical methods (e.g., histograms and scatterplots) in order to examine assumptions such as normality that underlie statistical models. Transformations will be used, if needed, to produce variables that conform to the distributional assumptions underlying the analytic techniques employed. Descriptive analyses will be performed in order to characterize the treatment groups and to confirm that the randomization resulted in no clinically significant group differences at baseline. Although emphasis will be on clinical significance, baseline comparisons will include t-tests or Wilcoxon rank sum tests as appropriate for interval variables and chi-square or Fisher's exact tests as appropriate for nominal variables to aid in the screening for baseline differences. Similarly, changes in clinical endpoints over time will be summarized within each treatment group using summary statistics including mean and median change scores, standard deviations and ranges. Pearson or Spearman rank correlation coefficients will be used to characterize associations among variables within treatment group. When summarizing across groups, partial correlations may be computed controlling for treatment group. For time-to-event outcomes (i.e., event-free survival), descriptive analyses will include construction of group specific Kaplan-Meier survival curves as appropriate

### 12.6.4 Secondary Endpoints

Secondary endpoints have been specified from several domains. Additional secondary endpoints include SOFA over time, time to the primary endpoint, critical care and hospital stay parameters (hospital length of stay (LOS), ICU and ICU-free days, ventilator days and –free days, vasopressor days and –free days). Analyses for these endpoints will generally be descriptive, with emphasis on characterizing clinical effect sizes. Nominal p-values will be presented. Categorical outcomes will be described using counts and percentages with nominal p-values determined through chi-square or exact methods. Critical care and hospital stay endpoints will be described using non-parametric approaches including using concordance statistics to characterize clinical effect sizes and Wilcoxon rank sum tests to determine nominal statistical significance. Methods appropriate for time-to-event endpoints including survival and life-table methods will be used for time-to-recovery endpoints.

## 12.7 Sub-group Analysis

Subgroup analysis will be performed. The primary subgroup analyses to be performed include:

Patients presenting with either Stage 2 or Stage 3 AKI.

By acuity of AKI (i.e., whether or not AKI is diagnosed at time of presentation of abdominal infection or surgically confirmed NSTI, or during the 48 hours from the suspected diagnosis of abdominal infection or surgical confirmation of NSTI).

By subject age ≥18 to ≤75 or >75 to ≤85 years old.

For these sub-group analyses, active dose versus placebo differences in likelihood of freedom from durable loss of renal function will be evaluated as well other selected secondary endpoints.

Other sub-groups to be evaluated will include patients who developed AKI up to ≤24 hours or 25-48 hours after the suspected diagnosis of abdominal infection or surgical confirmation of NSTI or if AKI diagnosed via creatinine criteria vs urine output criteria.

### 12.8 Assessment of Poolability Among Sites

Site poolability will be evaluated using a random effects meta-analysis approach using the R package ***metafor*** to implement the analysis[46]. True effects are assumed to be normally distributed with mean $\mu$ and variance $\tau^2$. By imposing a specified distribution on the site-to-site variability, i.e. a normal distribution with mean $\mu$ and variance $\tau^2$, sensitivity to small sample sizes in individual sites is reduced and the parameters reflecting the magnitude of site-to-site variability are naturally derived. The quantitative measure of the magnitude of heterogeneity is $I^2$ [47]. $I^2$ is the fraction of $\boldsymbol{\tau^2}$ that is due to site to site differences in treatment effects (effect size heterogeneity), as opposed to sampling variance. Fractions 25% and less are considered small. If there is significant site-to-site variability, the impact on this variability will be evaluated using a random effects logistic regression to test the null hypothesis that the likelihood of achieving freedom from durable loss of renal function is the same for treated and placebo patients accounting for a random site effect. Poolability according to baseline demographic, disease severity status, and number of levels treated will be evaluated using descriptive stratified analyses.

### 12.9 Analysis of Other Covariate Effects

Covariates will be assessed for potential confounding (due to lack of perfect randomization balance) or effect modification (subgroup efficacy heterogeneity) using multiple logistic regression. Covariates will include but are not limited to age, race, sex, site, and clinical severity scores at baseline. Other baseline variables in which randomization failed to produce adequate balance between groups will be examined in supporting analyses. This will be done through stratified analyses and/or multiple logistic regression. Covariate effects on estimates and interactions will be assessed to see if there is evidence of efficacy heterogeneity. Results from all subgroups analyses will be considered hypothesis-generating.

### 12.10 Multiplicity

There is a single primary hypothesis test utilizing a single clinical success endpoint, freedom from durable loss of renal function. Therefore, there is no issue with regard to multiplicity.

### 12.10.1Longitudinal Data

A number of secondary efficacy endpoints will be assessed over time including SOFA total score.

Where appropriate for continuous measures, statistical testing and estimation will be based on the results from a Mixed Model Repeated Measures (MMRM) analysis of covariance (ANCOVA) model. This model will include the baseline value of the outcome variable if appropriate. Other clinically relevant baseline variables predictive of outcome will be considered if there is missing outcome data over time. Inclusion of such covariates helps with the implicit imputation of missing values inherent in the MMRM approach. MMRM is a direct likelihood approach requiring specialized statistical software for optimizing the likelihood function. For this study, all MMRM parameters will be estimated using SAS PROC MIXED version 9.4 or higher [SAS Institute, Cary, NC]. The MMRM model is notable for its ability to include all available data from all eligible subjects and does not require their exclusion as in complete case analysis or arbitrary assignment of values as in LOCF. The MMRM model generally includes a factor for group by time interaction in order to allow group differences in mean values to vary over time. Inclusion of outcome data from all time points informs the implicit imputation of values missing at specific time points through the outcome covariance matrix. Inclusion of baseline covariates has potential for further reduction of potential bias due from missing values.

Specifically, MMRM will be used to compare mean values over time between the 0.50 mg/kg dose and placebo. Model parameters will be estimated using Restricted Maximum Likelihood[48,49] (REML) as implemented Proc Mixed [SAS Institute, Proc Mixed, SAS/STAT Software]. A generalized Satterthwaite approximation will be used to determine accurate estimates of denominator degrees of freedom for statistical tests. Analyses will characterize changes over time as functions of the baseline value, treatment group, time, and treatment by time interaction. Between-group differences at each time point will be evaluated using contrasts derived from mixed model parameter estimates. This approach produces inferences that are valid under the assumption of missing at random (MAR) which produces valid inference under broader assumptions than complete case analysis or analyses utilizing LOCF[50].

### 12.10.2Analysis of Event-time and Overall Survival

Time-to-event endpoints will be assessed in descriptive analyses using survival and life-table methods as appropriate. Analyses will include time to freedom from durable loss of renal function and time to at least durable loss of renal function. Similarly, overall survival through 90 days will be compared between groups using Kaplan-Meier survival curves. The significance of treatment differences will be assessed using log rank statistics.

## 12.11 Handling of Missing Data

### 12.11.1Intent-to-Treat

The purpose of intent-to-treat comparisons is to ensure that randomization is protected (i.e., all groups have comparable baseline characteristics and that any differences besides therapy are due to chance) and to preclude the possibility of bias due to selectively excluding

subjects from therapy groups. This is intended to avoid systematic differences among the groups attributable to factors other than therapy assignment[51]. Therefore, we will attempt to include all randomized patients in the primary effectiveness analysis, regardless of intervention or length of follow-up in the primary efficacy comparison, with the exception of subjects that are subsequently confirmed to not have Stage 2 or 3 AKI, abdominal sepsis or NSTI. Due to the critical nature of this indicated population, it is sometimes necessary to begin drug administration prior to disease confirmation. Subjects confirmed to not have abdominal sepsis or NSTI will be excluded from the mITT analysis set to be used in primary and secondary efficacy analysis but included in the As Treated analysis set to be used in primary safety analysis.

### 12.11.2LOCF of Day 28 Creatinine

In order to determine the primary endpoint, freedom from durable loss of renal function, Day 28 creatinine is necessary. Patients surviving to Day 28 or later but with missing Day 28 creatinine will have their Day 28 creatinine values determined through last observation carried forward (LOCF) of earlier values. Creatinine values will be confirmed 3 to 21 Days after Visit 9.

### 12.11.3SOFA Scores

SOFA scores over time will be assessed as 1) observed cases, 2) LOCF, and 3) using MMRM.

Individually missing SOFA component values due to non-measurement are conventionally assumed as normal and this convention will be followed for this study.

LOCF will not be applied to missing SOFA scores after patient death in analyses that employ LOCF to describe mean values of time. Therefore, analysis of SOFA mean values using LOCF will focus on morbidity rather than mortality.

Mixed model repeated measures analyses will utilize implicit imputed values for all missing values including those subsequent to patient death.

In categorical analyses including formulation of the secondary effectiveness endpoint, total SOFA score at Day 14 $\leq$ 1, LOCF is necessary to guarantee that every patient has a value at Day 14.

### 12.11.4Mixed Model Repeated Measures

As describe above, continuous measure observed over time including SOFA will be assessed using MMRM where possible. MMRM uses all available data and results in implicit imputations for missing data which are valid under MAR, a more general set of assumptions than missing completely at random (MCAR).

## 12.12 Safety Analysis

The primary safety measures are AEs (including SAEs), clinical safety laboratory, PE, vital signs through Day 28 and including determination of survival through Day 28.

The safety profiles will be compared between active and placebo groups using descriptive statistics as appropriate for continuous and categorical safety variables. Changes in

continuous safety measures such as laboratory values will be summarized by mean changes over time using descriptive statistics (mean, SD, median, minimum and maximum). The presence of clinically significant safety findings will be summarized by shift tables separately for each group using counts and percentages. AEs will be classified according to system organ class and preferred term and summarized by counts and percentages separately for those recorded at Screening (prior to drug administration) and those with onset on Day 1 or later. AEs will also be summarized by relationship to study drug, severity, and whether they are serious. Specific summaries will involve AEs and SAEs in the Infection/Infestation system organ class. Results from PEs will be tabulated for the Screening, Day 7, and Day 14. For each test, the number of patients evaluated, and the numbers and percentages of patients with Normal and Abnormal results will be tabulated. Vital signs including weight, temperature, systolic BP, diastolic BP, respiration rate, and heart rate will be summarized across time (Screening, Day 1, Day 2, Day 3, Day 7, and Day 14 separately by treatment group by N, Mean, and SD.

# 13. SOURCE DATA ACCESS, DATA MANAGEMENT AND DATA HANDLING

## 13.1 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the eCRF/electronic data capture (EDC) system for this study must be consistent with the patients' source documentation (i.e., medical records).

## 13.2 Database Management

Data Management services will be provided by the Sponsor or designee. The data management system will be specified in the Data Management Plan.

After the data have been entered and verified, various edit checks will be performed for the purpose of ensuring the accuracy, integrity and validity of the database. These edit checks may include:

- Range checks
- Consistency checks
- Sequence checks
- Protocol adherence checks

Queries generated from these checks will be sent to the investigational site for resolution, and the database will be updated to reflect query resolutions as appropriate.

AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary.

### 13.3 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the EDC system promptly. All source documents from which eCRF/EDC system entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments, ECG, and microbiological outcome.

Data that will be entered directly into the eCRF/EDC system are considered to be source data.

The original eCRF/EDC system entries for each patient may be checked against source documents at the study site by the Sponsor site monitor.

After review by the site monitor, completed eCRF/EDC system entries will be uploaded for data check by the Sponsor's data management CRO. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

The specific procedures to be used for data entry and query resolution using the EDC system/eCRF will be provided to study sites in a study manual. In addition, site personnel will receive training on the EDC system/eCRF.

### 13.4 Data Collection

The Investigators (and appropriately authorized staff) will be given access to an online web-based EDC system which is compliant with 21 CFR Part 11. This system is specifically designed for the collection of the clinical data in electronic format. Access and right to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the eCRF/EDC system.

The EDC system/eCRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the EDC system/eCRFs are to be completed as soon as possible (within 5 working days) after the patient's visit or assessment. The Investigator must verify that all data entries in the EDC system/eCRFs are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the EDC system/eCRFs.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved online. All discrepancies will be solved online directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Investigator will be required to electronically sign off the clinical data.

Data about all study drug dispensed to the patient will be tracked on the EDC system/eCRFs.

### 13.5 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare EDC system/eCRFs entries and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. EDC system/eCRFs entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained, and the study blind is respected.

Checking of the EDC system/eCRFs entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor of the necessary support at all times.

### 13.6 Archiving Study Records

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational Product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

## 14. QUALITY ASSURANCE

To comply with ICH GCP Guidelines, an independent audit at the study site may take place at any time during or after the study. The independent audit can be conducted by the Quality Assurance Department of the Sponsor or a regulatory authority. ICH GCP Guidelines state that investigational sites and all data, including source data, must be available for inspection by competent authorities. The Investigator shall inform patients that their medical records will be reviewed during these audits, however, pursuant to current HIPAA regulations; the patients' privacy must be respected. Sufficient prior notice will be provided to allow the Investigator to properly prepare for the audit.

# 15. GENERAL STUDY ADMINISTRATION

## 15.1 Ethical Aspects

### 15.1.1 Good Clinical Practices / Local Regulations

This study will be carried out according to the Declaration of Helsinki, the Notes for Guidance on Good Clinical Practice (2000) (CPMP/ICH/135/95), with ICH GCP, and any local applicable regulations.

The Sponsor will be responsible for reporting all serious, life-threatening or fatal adverse Investigational Product events with a causal relationship to the Investigational Product to appropriate regulatory agencies within their required timelines.

The Principal Investigator will ensure that this study is conducted in full compliance with the protocol, the Declaration of Helsinki, the ICH guideline for GCP, and all other applicable local laws and regulations. Compliance with these standards provides assurance that the rights, safety, and well-being of patients are protected.

In agreeing to the provisions of the protocol, these responsibilities are accepted by the Investigator.

## 15.2 Informed Consent

Prior to initiation of the study, the Investigator will provide the Sponsor with a copy of the investigational site's IRB/EC approved study ICF. The ICF must contain all elements required by ICH GCP (E6). The ICF must also adhere to local privacy requirements as well as any other elements required by state, local and institutional policies.

All prospective patients or the patient's LAR will be given a copy of the approved study ICF to read.

Before being admitted to the clinical study, the patient must have given written consent, or the LAR must have given phone/fax/email/e-consent or written consent to participate in the study, after the nature, scope, and possible consequences of the study (including insurance and other procedures for compensation in case of injury) have been explained in an understandable form by the Investigator or nominee.

It will be pointed out that patients/LARs can refuse to participate in the study or withdraw from the study without prejudice to further care and treatment.

Ample time and opportunity will be allowed for each patient/LAR to inquire about details of the study and to decide whether or not to participate in the study.

Both the patient/LAR and the person who conducts the informed consent discussion will sign and personally date the document. The acquisition of informed consent should be documented in the patients' medical records.

Where consent has been obtained from a LAR, if the patient is deemed by the Investigator able to provide informed consent on their own behalf any time during the study period,

informed consent from the patient will be obtained. The patient has the ability to withdraw from the study at any time, for any reason.

Patients/LARs will be informed of any significant new finding which arises during the course of the research that may affect their decision to continue participation.

### 15.3 Institutional Review Board / Ethics Committee

The protocol will be submitted for approval to the appropriate IRB/EC. Prior to initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/EC approval of the protocol and study ICF. This approval letter will identify the study ICF by date or version number, and the study protocol by protocol number, title, and date. The Investigators will receive all the documentation needed for submitting the present protocol to the IRB/EC. The composition of the IRB/EC will also be provided to the Sponsor. If approval is suspended or terminated by the IRB/EC, the Investigator will notify the Sponsor immediately.

It is the responsibility of the Investigator to report study progress to the IRB/EC as required or at intervals not greater than one year.

The Principal Investigator or his/her nominee will be responsible for reporting any SAEs to the IRB/EC as soon as possible, and in accordance with the guidelines of the IRB/EC.

#### 15.3.1 Conditions for Modifying the Protocol

No changes (amendments) to the protocol may be implemented without prior approval from the Sponsor and the appropriate IRB/EC, except where necessary to eliminate an immediate hazard to patients, or when the change involves only logistical or administrative aspects of the study.

Once the final protocol has been issued and signed by the Investigator and the authorized signatories, it shall not be informally altered. Protocol amendments are alterations to a legal document and have the same legal status. Therefore, they must pass through appropriate steps before being implemented. In general, any important change that theoretically increases risk to patients constitutes an amendment. Protocol modifications that impact on patients' safety or the validity of the study will be approved by the IRB/EC. Minor changes such as administrative changes may be documented without approval, if permissible by the IRB/EC.

The Investigator will not modify the protocol without first obtaining the concurrence of the Sponsor in writing. Should the Sponsor modify the protocol, they will provide the Investigator with a written amendment. It is the responsibility of the Investigator to submit the amendment to the IRB/EC for their approval; written approval should be obtained, and a copy provided to the Sponsor. The Sponsor is responsible for determining whether or not the local regulatory authority must be notified of the protocol change. Completed and signed protocol amendments will be circulated to all those who were on the circulation list for the original protocol.

The original signed copy of amendments will be kept in the Study File with the original protocol. It should be noted that where an amendment to the protocol substantially alters

the study design or the potential risks to the patient, each patient's consent to continue participation should be obtained.

If a protocol amendment requires changes to the ICF, the revised ICF, prepared by the Investigator, must be approved by the IRB/EC.

### 15.4 Patient Confidentiality

The anonymity of participating patients must be maintained. Patients will be identified on eCRF/EDC system and other documents submitted to the Sponsor by their patient number, initials and/or birth date, not by name. Documents not to be submitted to the Sponsor that identify the patient (e.g., the signed informed consent) must be maintained in confidence by the Investigator. A Data Protection Officer (DPO) will be used in this study by MyData-TRUST.

### 15.5 Investigator Responsibilities

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, current ICH GCP Guidelines, and applicable regulatory requirements. These documents set forth that the informed consent of the patients is an essential precondition for participation in the clinical study.

### 15.6 Laboratory Accreditation

Any laboratory facility to be used for analysis of routine clinical laboratory samples required by this protocol should provide reference values and/or normal ranges for the test results used in conducting this protocol.

### 15.7 Study Initiation

All personnel expected to be involved in the conduct of the study will undergo an orientation to include review of the study protocol, instructions for record completion, and overall responsibilities.

#### 15.7.1 Study Completion

The Investigator will complete the study and complete all patients' eCRFs in satisfactory compliance with the protocol within 2 weeks after study completion. Continuation of this study beyond this time must be agreed upon in writing by both the Investigator and Sponsor and may be implemented without amendment to the protocol.

#### 15.7.2 Study Termination

An initiative for center closure or study termination can be taken at any time either by the Sponsor/designee or by the Investigator, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for such action taken by the Sponsor/designee include, but are not limited to:

- Successful completion of the study at the center
- The required number of patients for the study has been recruited
- Failure of the Investigator to comply with the protocol, the Sponsor's/designee's procedures, or ICH GCP Guidelines

- Safety concerns
- Sufficient data suggesting lack of efficacy
- Inadequate recruitment of patients by the Investigator

# 16. CONFIDENTIAL INFORMATION

## 16.1 Confidential Information

All information obtained as a result of this study or during the conduct of this study concerning Atox Bio operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the Atox Bio to the Investigator and not previously published, is considered confidential and remains the sole property of the Atox Bio. The Investigator agrees to use this information only to conduct this study and will not use it for other purposes without Atox Bio prior written consent.

## 16.2 ClinicalTrials.gov Study Registration

This clinical study, ATB-203, will be registered on www.ClincalTrials.gov prior to enrollment of the first patient. Patients are to be made aware of this study registration through the informed consent process prior to study participation. Final study results will be posted on ClinicalTrial.gov according to US regulatory guidelines.

## 16.3 Publication Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance. Details are provided in a separate document.

## 17. REFERENCES

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# 18. APPENDICES

## 18.1 Appendix A - Study Visits and Procedures

| Visit | 1<br>Screening[a] | 2<br>Day 1 | 3<br>Day 2 | 4<br>Day 3 | 5<br>Day 7 ±1 day | 6<br>Day 10 ±1 day | 7<br>Day 14 ±1 days | 8<br>Day 21 ±1 days | 9<br>Day 29 +3 days | 10<br>3 to 21 Days after Visit 9 | 11<br>Day 90 +5 days |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | | | | | |
| Demographics | X | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| Lesion History (NSTI) | X | | | | | | | | | | |
| Concomitant Medications[b] | → | → | → | → | → | → | → | → | → | | |
| Weight & Height[c] | X | | | | X | | X | | X | | |
| Fluid Balance (input/output) | | → | → | → | → | | | | | | |
| Detailed Urine Output[d] | → | → | → | → | → | | | | | | |
| Vital Signs[e] | X | X | X | X | X | X | X | X | X | | |
| Physical Examination (PE) | X | | | | X | | X | | | | |
| Interim PE (symptom-driven) | | X | | X | | X | | | | | |

[a] Screening period can be 48 hours after suspected diagnosis of abdominal infection
[b] See Section 9.2.5 for instruction on level of detailed information required for recording concomitant medications
[c] Height will be taken only at screening or first time that patient height can be measured
[d] Urine output is required for Days 1-7 (while the patient is in the ICU or step-down unit (or equivalent); patients on a general ward only monitor urine output if a Foley catheter is in place as part of standard of care) to assess for development or resolution of acute kidney injury
[e] Systolic & diastolic blood pressure, mean arterial pressure, heart rate, respiration rate, temperature; (first set of vitals on that visit day)

| Visit | 1<br>Screening[a] | 2<br>Day 1 | 3<br>Day 2 | 4<br>Day 3 | 5<br>Day 7 ±1 day | 6<br>Day 10 ±1 day | 7<br>Day 14 ±1 days | 8<br>Day 21 ±1 days | 9<br>Day 29 +3 days | 10<br>3 to 21 Days after Visit 9 | 11<br>Day 90 +5 days |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Baseline Signs & Symptoms[f] | X | | | | | | | | | | |
| Blood Chemistry[g] | X[h] | X[i] | X[j] | X[i] | X | X[j] | X | X[j] | X[k] | X[j] | X[j] |
| Spot Urine Albumin/ Creatinine[l] | X | X | | X | X | | X | | X | | X |
| Standard C-Reactive Protein[m] | X | | | | X | | X | | X | | |
| Blood Hematology[n] | X | X | | X | X | | X | | X | | |
| Pregnancy Test (if applicable)[o] | X | | | | | | | | | | |
| Serum for Immunogenicity[p] | X | | | | | | X | | X | | X |
| Urine and Plasma for Storage[q] | X | | X | | X | | | | | | |

[f] Adverse events reported from ICF signature to Reltecimod administration
[g] Glucose; Electrolytes - Sodium, Potassium, Calcium; Phosphorus, Chloride, Bicarbonate; Renal function tests – Urea/BUN, Creatinine; Liver function tests – Albumin, Bilirubin Total, Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatase (ALP), Protein Total. In case of abnormal results at the end of the study the results should be followed by the investigator until the abnormalities are resolved or determined as stabilized
[h] If AKI diagnosis not established at time of initial evaluation for abdominal infection, then obtain creatinine every 6 hours for up to 48 hours after suspected or confirmed diagnosis of abdominal infection to identify development of AKI
[i] Only creatinine and bilirubin
[j] Only creatinine
[k] Creatinine and albumin only
[l] Obtain urine specimen for spot albumin/creatinine ratio. First morning void is preferred
[m] Use standard CRP test (do not use cardiac or high-sensitivity CRP)
[n] Complete blood count including platelet count and white blood cell differential
[o] Preferably the fastest pregnancy test method (urine or blood)
[p] 6 mL blood for serum for storage (for immunogenicity testing) at screening, Days 14 29, and 90
[q] Obtain 5 mL urine and 5 mL blood for plasma for storage for AKI biomarker analysis. Second sample to be collected 24±6 hours (Day 2) after study medication administration. Final sample to be obtained at Day 7

| Visit | 1<br>Screening[a] | 2<br>Day 1 | 3<br>Day 2 | 4<br>Day 3 | 5<br>Day 7 ±1 day | 6<br>Day 10 ±1 day | 7<br>Day 14 ±1 days | 8<br>Day 21 ±1 days | 9<br>Day 29 +3 days | 10<br>3 to 21 Days after Visit 9 | 11<br>Day 90 +5 days |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Systemic Inflammatory Biomarkers<br>• RNA[r]<br>• Cytokines / Chemokines[s] | X<br>X | X<br>X | X<br>X | X<br>X | | | | | | | |
| Arterial Blood Gases (if applicable) | X | X | | X | X | | X | | | | |
| SpO2 and FiO2 (if arterial blood gases not indicated or unable to obtain) | X | X | | X | X | | X | | | | |
| Peritoneal Fluid, Tissue or Abscess Fluid for Abdominal Infection, or Tissue for NSTI for Microbiology | X | | | | | | | | | | |
| Inclusion & Exclusion[t] | X | | | | | | | | | | |
| Randomization | X | | | | | | | | | | |

[r] 5 mL (2 x 2.5 mL) of whole blood to be collected at screening, Day 1 at 4 to 6 hours post-dose, Day 2 at 24 ±4 hours post dose, Day 3 at 48 hours ±4 hours post-dose, and Day 4 72 ±4 hours post dose. Complete blood count with white blood cell differential to be obtained at same time of whole blood for genomic profile sample

[s] Systemic Biomarkers will be taken at screening, 4 to 6 hours, 24±4, 48±4 and 72±4 hours post drug administration; However, if practical consideration allow collection of fewer plasma samples, this will not be considered a protocol deviation. Systemic blood inflammatory biomarkers will include serum cytokines or chemokines such as (but not limited to): IL-6, IL-8, INF-γ, TNF-α, IL-17A, IL-3 and RANTES.

[t] Should be verified twice: a full list of criteria will be verified once before instructing the pharmacist to prepare study drug and a second time immediately before study drug administration according to a partial list to include verification that 6 hours has not elapsed from time to study drug administration

| Visit | 1<br>Screening[a] | 2<br>Day 1 | 3<br>Day 2 | 4<br>Day 3 | 5<br>Day 7 ±1 day | 6<br>Day 10 ±1 day | 7<br>Day 14 ±1 days | 8<br>Day 21 ±1 days | 9<br>Day 29 +3 days | 10<br>3 to 21 Days after Visit 9 | 11<br>Day 90 +5 days |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reltecimod / Placebo Administration | | X | | | | | | | | | |
| Blood Culture[u] | X | | | | | | | | | | |
| Adverse Events / Serious Adverse Events[v] | [w] → | | | | | | | | | | |
| Lesion Assessment (NSTI)[x] | X | X | X | X | X | X | X | | | | |
| Collect data on Additional Amputations (NSTI) | → | | | | | | | | | | |
| Collect Data on Acute Renal Replacement Therapy | → | | | | | | | | | | |
| Collect Data on Renal Imaging | → | | | | | | | | | | |
| Collect Data on Additional Renal Procedures (e.g., Renal Biopsy) | → | | | | | | | | | | |
| Record any Follow-up Surgical or | | → | | | | | | | | | |

[u] Blood culture for both aerobic and anaerobic bacteria will be repeated during the study in case of new systemic infection suspicion
[v] Adverse events including SAEs will be collected from obtaining ICF through day 28; AEs that are not resolved should be followed-up until resolution or until determined as stable and due to known cause
[w] AEs of Screening are baseline AEs (not TEAE) starting after obtaining ICF until study drug administration
[x] Assess lesion status (healing/progression/significant change in appearance) if accessible for visible assessment at time of debridement or routine dressing change

| Visit | 1<br>Screening[a] | 2<br>Day 1 | 3<br>Day 2 | 4<br>Day 3 | 5<br>Day 7 ±1 day | 6<br>Day 10 ±1 day | 7<br>Day 14 ±1 days | 8<br>Day 21 ±1 days | 9<br>Day 29 +3 days | 10<br>3 to 21 Days after Visit 9 | 11<br>Day 90 +5 days |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Interventional Radiologic Procedures for Previously Documented Abdominal Infection | | | | | | | | | | | |
| Evaluation of Adequacy of Antimicrobial Treatment | | | | X | | | | | | | |
| Critical Care and Hospital Stay Parameters[y] | | → | → | → | → | → | → | → | → | | |
| SOFA Score[z] | X | X[aa] | | X | X | | X | | | | |
| APACHE II Score[bb] | X | | | | | | | | | | |
| Survival | | → | → | → | → | → | → | → | → | → | → |
| Hospital Readmissions | | | | | | | | | X | | X[cc] |

[y] Hospital length of stay (days), ICU stay (days), ICU free days, mechanical ventilation days/mechanical ventilation free days

[z] Screening SOFA: To include measurements of 6 organ system: cardiovascular, respiratory, renal, coagulation, GI/hepatic and CNS (To include evaluation of oxygenation either directly by arterial blood gas test or by calculation of $PaO_2$ from $SpO_2$, in case it is not possible to obtain arterial blood to determine the SOFA respiratory parameter)

[aa] Subsequent SOFA measurement (Days 1, 3, 7, and 14): taken once a day, in the morning adjusted to the time of normal routine assessment activities. To be calculated retrospectively. The following blood samples must be taken: CBC with platelet count, serum creatinine and bilirubin. In addition, clinical parameters should be evaluated and recorded (see Section 18.3)

[bb] For the required laboratory and clinical parameters (see Section 18.2 of the protocol)

[cc] Capture data on any readmissions within 30 days of original hospital discharge

## 18.2 Appendix B – APACHE II Score

### APACHE II Score:

- For each variable used in the APACHE II Score, the value from the previous 24 hours yielding the most points should be used
- Since it is not possible to assess the Glasgow Coma Scale (GCS) in patients who are sedated and paralyzed, by convention it is regarded as normal, unless it is known that there was a brain injury prior to sedation, as in the case of head injury (but not confusion associated with tiredness, hypoxia, etc.). This will result in a GCS of 15 and a neurologic score of 0 (zero).
- Chronic Health Evaluation

If any of these conditions are marked "Y", assign points based on the patient's condition at the time of ICU admission (or in the 24-hour period prior to screening) - See Section C on last page.

| *Organ insufficiency or immuno-compromised state must have been evident prior to this hospital admission and conform to the following criteria.* | |
|---|---|
| LIVER: Biopsy-proven cirrhosis and documented portal hypertension. or episodes of past upper GI bleeding attributed to portal hypertension, or prior episodes of hepatic failure/encephalopathy/coma. | Y N |
| CARDIOVASCULAR: New York Heart Association Class IV. | Y N |
| RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, (i.e., unable to climb stairs or perform household duties); or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mm Hg), or respirator dependency. | Y N |
| RENAL: Receiving chronic hemo- or peritoneal dialysis. | Y N |
| IMMUNO-COMPROMISED: | |
| (1) The patient has received therapy that suppresses resistance to infection, eg immuno-suppressive agents, chemotherapy, radiation, long term low dose steroids, 10 mg/day prednisone for >1 month prior to hospitalization) or recent high dose steroids (> 15 mg/kg/day of hydrocortisone or >3 mg/kg/day of methylprednisolone for >5 days). | Y N |
| (2) The patient has a disease that is sufficiently advanced to suppress resistance to infection, eg leukemia, lymphoma, AIDS, documented diffuse metastatic cancer. | Y N |

| Physiologic Variable | | HIGH ABNORMAL RANGE (Check one range per variable and write the severity score in the column to the right. Note: use the worst possible score for all variables, except for the GCS score.) | | | | | LOW ABNORMAL RANGE | | | | Severity Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Severity Points | +4 | +3 | +2 | +1 | 0 | +1 | +2 | +3 | +4 | |
| 1 | Temperature – rectal (°C) | ☐ ≥41° | ☐ 39-40.9° | | ☐ 38.5°-38.9° | ☐ 36°-38.4° | ☐ 34°-35.9° | ☐ 32°-33.9° | ☐ 30°-31.9° | ☐ ≤29.9° | |
| 2 | Mean Arterial Pressume (mmHg) | ☐ ≥160 | ☐ 130-159 | ☐ 110-129 | | ☐ 70-109 | | ☐ 50-69 | | ☐ ≤49 | |
| 3 | Heart Rate (Ventricular Response) | ☐ ≥180 | ☐ 140-179 | ☐ 110-139 | | ☐ 70-109 | | ☐ 55-69 | ☐ 40-54 | ☐ ≤39 | |
| 4 | Resp. Rate (non-ventilated or ventilated) | ☐ ≥50 | ☐ 35-49 | | ☐ 25-34 | ☐ 12-24 | ☐ 10-11 | ☐ 6-9 | | ☐ ≤5 | |
| 5 | Oxygenation:<br>a. $FIO_2 \geq 0.5$ record $A{\cdot}aDO_2$* | ☐ ≥500 | ☐ 350-499 | ☐ 200-349 | | ☐ <200 | | | | | |
| | b. $FIO_2 < 0.5$ record only $PaO_2$ | | | | | ☐ $PaO_2$>70 | ☐ $PaO_2$ 61-70 | | ☐ $PaO_2$ 55-60 | ☐ $PaO_2$<55 | |
| 6 | Arterial pH | ☐ ≥7.7 | ☐ 7.6-7.69 | | ☐ 7.5-7.59 | ☐ 7.33-7.49 | | ☐ 7.25-7.32 | ☐ 7.15-7.24 | ☐ <7.15 | |
| 7 | Serum Sodium (mmol/L) | ☐ ≥180 | ☐ 160-179 | ☐ 155-159 | ☐ 150-154 | ☐ 130-149 | | ☐ 120-129 | ☐ 111-119 | ☐ ≤110 | |
| 8 | Serum Potassium (mmol/L) | ☐ ≥7 | ☐ 6-6.9 | | ☐ 5.5-5.9 | ☐ 3.5-5.4 | ☐ 3-3.4 | ☐ 2.5-2.9 | | ☐ <2.5 | |
| 9 | Serum Creatinine (µmol/L)<br>(double point score for acute renal failure) | ☐ ≥309.4 | ☐ 176.8-309.3 | ☐ 132-177 | | ☐ 53-133 | | ☐ <53 | | | |
| 10 | Hematocrit (%) | ☐ ≥60 | | ☐ 50-59.9 | ☐ 46-49.9 | ☐ 30-45.9 | | ☐ 20-29.9 | | ☐ <20 | |
| 11 | White Blood Count (total/$mm^3$)<br>(in 1000s) | ☐ ≥40 | | ☐ 20-39.9 | ☐ 15-19.9 | ☐ 3-14.9 | | ☐ 1-2.9 | | ☐ <1 | |
| 12 | Glasgow Coma Score (GCS)<br>Score=15 minus actual GCS | Eye | Verbal | Motor | GCS Total (= Eye + Verbal + Motor) | | | | (Note: The best GCS used for the 1st 24 hours) | | (15 - GCS Total ) |
| A=Total ACUTE PHYSIOLOGY SCORE (APS): Total severity points indicated for Variables 1-12 in the column to the right. | | | | | | | | | | | |
| | Serum $HCO_3$ (venous-mmol/L)<br>(Use in place of variable 5 if no ABGs) | ☐ ≥52 | ☐ 41-51.9 | | ☐ 32-40.9 | ☐ 22-31.9 | | ☐ 18-21.9 | ☐ 15-17.9 | ☐ <15 | |

* $A{\cdot}aDO_2 = [(FiO_2\ (713)-(PaCO_2/0.8)]-PaO_2$

## 18.3 Appendix C – SOFA Score

| Value | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| Respiratory<br>$PaO_2/FiO_2$[1] | >400 | ≤400 | ≤300 | ≤200 with respiratory support | ≤100 with respiratory support |
| Coagulation<br>Platelets | >150 | ≤150 | ≤100 | ≤50 | ≤20 |
| GI<br>Total Bilirubin[3] | <1.2 | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | ≥12.0 |
| Cardiovascular[2] | No hypo-tension | MAP <70 | Dopa ≤5<br>PE <100 | Dopa > 5<br>Epi ≤ 0.1<br>NE ≤ 0.1<br>PE 100-300 | Dopa>15<br>Epi>0.1<br>NE>0.1<br>PE>300<br>VP>0.01 |
| Neuro<br>GCS | 15 | 13-14 | 10-12 | 6-9 | <6 |
| Serum Creatinine[3]<br>OR<br>Urine Output | <1.2 | 1.2-1.9 | 2.0-3.4 | 3.5-4.9<br><br><500cc/ day | ≥5.0<br><br><200cc/ day |

1. For patients on supplemental oxygen via nasal cannula, nasopharyngeal catheter or mask and for converting SpO2 values to PaO2 use the attached oxygen conversion tables.

2. Doses of dopamine (Dopa), epinephrine (Epi), norepinephrine (NE) are in micrograms/kg/min; phenylephrine (PE) is micrograms/min; vasopressin (VP) is U/min. Vasopressors must have been administered for at least one hour.

3. Total bilirubin and creatinine are in mg/dL.

## Oxygen Conversion Tables

| $SpO_2$ (%) | $PaO_2$ (mmHg) |
|---|---|
| 80 | 44 |
| 81 | 45 |
| 82 | 46 |
| 83 | 47 |
| 84 | 49 |
| 85 | 50 |
| 86 | 52 |
| 87 | 53 |
| 88 | 55 |
| 89 | 57 |
| 90 | 60 |
| 91 | 62 |
| 92 | 65 |
| 93 | 69 |
| 94 | 73 |
| 95 | 79 |
| 96 | 86 |
| 97 | 96 |
| 98 | 112 |
| 99 | 145 |

## Estimating FiO2

| Method | $O_2$ flow | Estimated FiO2 (%) |
|---|---|---|
| Nasal cannula | 1 | 24 |
| | 2 | 27 |
| | 3 | 30 |
| | 4 | 33 |
| | 5 | 36 |
| | 6 | 40 |
| | | |
| Nasopharyngeal catheter | 4 | 40 |
| | 5 | 50 |
| | 6 | 60 |
| | | |
| Face mask | 5 | 40 |
| | 6-7 | 50 |
| | 7-8 | 60 |
| | | |
| Face mask with reservoir | 6 | 60 |
| | 7 | 70 |
| | ≥8 | 80 |

## 18.4 Appendix D – Glasgow Coma Scale

| **Enter one score for each response (Eyes, Motor and Verbal).** | | | |
|---|---|---|---|
| Eyes Open | Motor Responses | Verbal – Non-Intubated | Verbal – Intubated |
| 4 = spontaneously<br>3 = to verbal<br>2 = to painful stimuli<br>1 = no response | 6 = to verbal command<br>5 = localized to pain<br>4 = withdraws to pain<br>3 = decorticate<br>2 = decerebrate<br>1 = no response | 5 = oriented and converses<br>4 = disoriented and talks<br>3 = inappropriate words<br>2 = incomprehensible words<br>1 = no response | 5 = seems able to talk<br>3 = questionable ability to talk<br>1 = generally unresponsive |
| Total Glasgow Coma Score (Eyes + Motor + Verbal) | | | |

## 18.5 Appendix E – AKI Staging (KDIGO Criteria)

| Stage | Serum Creatinine | Urine Output[1] |
|---|---|---|
| 1 | 1.5-1.9 times baseline<br>OR<br>≥0.3 mg/dL increase | < 0.5 mL/kg/h for 6 h |
| 2 | 2-2.9 times baseline | < 0.5 mL/kg/h for 12 h |
| 3 | 3 times baseline<br>OR<br>Increase in serum creatinine to ≥4 mg/dL<br>OR<br>Initiation of renal replacement therapy | < 0.3 mL/kg/h for 24 h<br>OR<br>Anuria for ≥12 h |

1. Urine output should be calculated using IBW (using the Miller Formula). Urine output for patients in a non-ICU setting (e.g., general ward) can only be used to assess AKI staging if urine collection (and subsequent recording) is obtained from patients with a Foley catheter in place as part of standard of care.

## 18.6 Appendix F – Twice the Serum Creatinine for Age, Race, and Gender

| Age (years) | Black Males mg/dL (µmol/L) | Other Males mg/dL (µmol/L) | Black Females mg/dL (µmol/L) | Other Females mg/dL (µmol/L) |
|---|---|---|---|---|
| **20 – 24** | 3.0 (266) | 2.6 (230) | 2.4 (212) | 2.0 (166) |
| **25 – 29** | 3.0 (266) | 2.4 (212) | 2.2 (194) | 2.0 (166) |
| **30 – 39** | 2.8 (248) | 2.4 (212) | 2.2 (194) | 1.8 (160) |
| **40 – 54** | 2.6 (230) | 2.2 (194) | 2.0 (176) | 1.8 (160) |
| **55 – 65** | 2.6 (230) | 2.2 (194) | 2.0 (176) | 1.6 (142) |
| **>65** | 2.4 (212) | 2.0 (166) | 1.8 (160) | 1.6 (142) |

Bellomo R, Ronco C, Kellum JA et al. Acute renal failure – definition, outcome, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI)Group. Crit Care 2004;8: R204-212.

## 18.7 Appendix G - Immunosuppressive Agents

| **Immunosuppressive Agent[a]** | **Upper Limit Dosage Use** |
|---|---|
| **1. Corticosteroid** | > 40 mg/day of prednisone or its equivalent daily for > 2 weeks |
| **Equivalent Dose (mg)** | |
| a) Prednisone | 40 mg |
| b) Hydrocortisone | 160 mg |
| c) Methylprednisolone | 32 mg |
| d) Dexamethasone | 6 mg |
| e) Cortisone | 200 mg |
| f) Betamethasone | 4.8 mg |
| 2. Methotrexate (Rheumatrex, Trexall) | Excluded at any dose |
| 3. Leflunomide (Arava)/Teriflunomide (Aubagio) | Acceptable if being used as monotherapy |
| 4. Cyclophosphamide (Cytoxan) | Excluded at any dose |
| 5. Cyclosporine A | Excluded at any dose (ophthalmic formulation (Restatis) is permitted) |
| 6. FK506 (Tacrolimus) | Excluded at any dose (optical formulation (Protopic) is permitted) |
| 7. Azathioprine | Excluded at any dose |
| 8. Cancer Chemotherapy | Patients receiving cancer chemotherapy in the previous 4 weeks are excluded |
| 9. Mycophenolate Mofetil (MMF) (CellCept) | Excluded at any dose (all solid organ and bone marrow transplant patients are excluded) |
| 10. Sirolimus (Rapamycin, Rapamune) | Excluded at any dose |
| 11. Everolimus (Certican) | Excluded at any dose |
| 12. Temsirolimus (Torisel) | Excluded at any dose |
| 13. Gusperimus | Excluded at any dose |

| | |
|---|---|
| 14. Thalidomide | Patients receiving Thalidomide within the last 72 hours are excluded. |
| **Immunosuppressive Agent[a]** | **Upper Limit Dosage Use** |
| **Biologics** | |
| (a) Anti-tumor necrosis factor (TNF) agents<br>- Entanercept (Enbrel)<br>- Entanercept (Enbrel)<br>- Afelimomab (Fab 2)<br>- Infliximab (Remicade)<br>- Certolizumab (Cimzia)<br>- Golimumab (Simponi) | Patients receiving Anti-TNF drugs within the last 8 weeks are excluded. |
| (b) Interleukin-1 Receptor Antagonist (IL-1RA)<br>- Kineret | Patients receiving IL-1RA within the last 8 weeks are excluded. |
| (c) CTLA-4 Fusion Protein<br>- Abatacept (Orencia)<br>- Alefacept (Amevive)<br>- Belatacept (Nulojix) | Patients receiving CTLA-4 Fusion protein within the last 8 weeks are excluded. |
| (d) Anti-CD20<br>- Rituximab (Rituxan/MabThera)<br>- Obintuzumab (Gazyva)<br>- Ocrelizumab (Ocrevus)<br>- Ofatumumab (Arzerra) | Patients receiving Anti-CD20 drugs within the last 2 years are excluded**.** |
| (e) Anti-CD52<br>- Alemtuzumab (Campath) | Patients receiving Anti-CD52 drugs within the last 2 years are excluded. |
| (f) Anti-IL2<br>- Daclizumab (Anti-Tac, Zenapax)<br>- Basiliximab (Simulect) | Patients receiving Anti-IL2 drugs within the last 2 years are excluded. |

| | |
|---|---|
| (g) Anti-IL6<br>- Tocilizumab (Actemra/RoActemra) | Patients receiving Anti-IL-6 drugs in the last 2 years are excluded. |
| (h) Anti-IL12/13<br>- Ustekinumab (Stelara) | Patients receiving Anti-IL 12/13 drugs in the last 2 years are excluded. |
| (i) Anti-BAFF (B-cell activating factor)<br>- Belimumab | Patients receiving Anti-BAFF drugs in the last 8 weeks are excluded. |
| (j) Integrin Inhibitor<br>- Natalizumab (Tysarbi) | Patients receiving Integrin Inhibitor drugs in the last 2 years are excluded. |
| (k) Anti-CTLA 4<br>- Ipilimumab | Patients receiving Anti-CTLA 4 drugs in the last 8 weeks are excluded. |
| (l) Other Interleukins<br>- Aldesleukin (Proleukin)<br>- Canakinumab (Ilaris)<br>- Oprelvekin (Neumega) | Patients receiving any of these Interleukin drugs in the last 2 years are excluded. |
| (m) Anti-PDL1<br>- Avelumab (Bavencio) | Patients receiving any Anti-PDL1 drugs in the last 2 years are excluded. |
| (n) Other Selective Immunosuppressants<br>- Muromonab or OKT-3:<br>- Efalizumab (Raptiva): anti-CD11a<br>- Fingolimod (Gilenya): Sphingosine 1-phosphate receptor modulator<br>- Eculizumab (Soliris): anti-complement protein C5<br>- Tofacitinib (Xeljanz): JAK-STAT Inhibitor | Patients receiving any of these drugs in the last 3 months are excluded. |

| | |
|---|---|
| - Apremilast (Otezla): PDE-4 inhibitor<br><br>- Vedolizumab (Entyvio): Integrin $\alpha_4\beta_7$ | Patients receiving any of these drugs in the last 2 years are excluded. |

[a] For agents not listed, patients should be off such therapies for a time sufficient to restore immune function.