CLINICAL STUDY REPORT

Study 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)
Investigational Product:	Reltecimod
Indication Studied:	Sepsis-associated acute kidney injury (SA-AKI)
Description of Study:	Phase 3, randomized, parallel-group study to evaluate the safety and efficacy of reltecimod in patients with SA-AKI.
Name of Sponsor:	Atox Bio Ltd. 8 Pinhas Sapir St. Weizmann Science Park Ness Ziona, 7403631 Israel
Protocol Number:	ATB-203
Trial Registry Number(s):	IND number: 128927 EudraCT number: 2018-002547-29
Development Phase:	Phase 3
First Patient Enrolled:	23 May 2018
Date of Early Termination:	21 October 2019
Last Patient Completed:	14 December 2019
Coordinating Investigator:	Azra Bihorac, MD, MS, FCCM, FASN Division of Nephrology, Hypertension, & Renal Transplantation Department of Medicine University of Florida, Gainesville, FL, USA
Sponsor Signatory:	Wayne Dankner, MD Chief Medical Officer, Atox Bio 1000 Park Forty Plaza, Suite 360 Durham NC 27713
GCP Compliance:	This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCP), including the archiving of essential documents as well as the ethical principles of the Declaration of Helsinki.
Report Version and Date:	Version 1, 06 August 2020

SIGNATURE PAGE

Study 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)
Name of Sponsor:	Atox Bio Ltd.
Protocol Number:	ATB-203
Sponsor's Responsible Medical Officer:	Wayne M Dankner, MD Chief Medical Officer, Atox Bio 1000 Park Forty Plaza, Suite 360 Durham, NC, USA
Date of the Report:	06 August 2020

I have read this report and confirm that, to the best of my knowledge, it accurately describes the conduct and results of the study.

Wayne M Dankner

Signature

06 AUG 2020

Date

2.0 SYNOPSIS

Name of Sponsor/Company:

Atox Bio Ltd.

Name of Finished Product:

Reltecimod for injection lyophilized product for intravenous (IV) injection

Name of Active Ingredient:

Reltecimod, a sodium salt of 10 amino acids synthetic peptide

Title of Study:

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)

Investigators and Study Centers:

The study was conducted at 70 qualified study centers with 67 Principal Investigators in the United States (US), Belgium, France, and the Netherlands of which 26 study centers enrolled at least 1 patient in the US and France.

Publications:

None

Study Period:	**Phase of Development:**
23 May 2018 (First Patient Enrolled) – 14 December 2019 (Last Patient Completed)	3

Background:

Acute kidney injury (AKI) is one of the most serious and common health complications in the critical care setting (intensive care unit [ICU]). Acute kidney injury is associated with a mortality rate of 60%, and despite advances in supportive care, mortality rates associated with AKI remain high. Depending on AKI severity, patients may spend a long time in the ICU and hospital and may develop chronic kidney disease (CKD) or end stage kidney failure requiring long-term dialysis treatment or kidney transplantation.

Acute kidney injury is a major complication of sepsis, and sepsis is regarded as the foremost precipitant of AKI. Sepsis-associated AKI (SA-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. 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.

Study ATB-203 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to assess the safety and efficacy of a 0.5mg/kg dose of reltecimod compared to placebo in the treatment of SA-AKI.

Reltecimod (previously known as AB103 or p*2TA*) the sodium salt of a synthetic peptide antagonist that consists of 10 amino acids and has homology to amino acid residues 8 to 15 of the T-lymphocyte molecule CD28, residues that are part of its homodimer interface. Reltecimod was designed to target the co-stimulatory pathway and interfere with the first steps of hyperinflammation.

Due to slow enrollment and after reviewing data from the ATB-202 study (Phase 3, randomized, double-blind, placebo-controlled, parallel-group study of reltecimod as compared to placebo in patients with necrotizing soft tissue infection [NSTI]), Atox Bio believed that restructuring the ATB-203 protocol was necessary for reltecimod

to be successful in patients with SA-AKI. Additional enrollment in the ATB-203 study was stopped and the study was terminated.

Objectives:

Primary Objectives

- 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]; calculated using the Modification of Diet in Renal Disease [MDRD] formula; relative to 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 0.5mg/kg to patients diagnosed with SA-AKI.

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 rate of resolution of organ dysfunction (resolution of organ dysfunction was defined as having a Sequential Organ Failure Assessment [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 following critical care and hospital stay parameters in patients with sepsis and AKI:
  - Hospital length of stay (LOS)
  - ICU LOS
  - ICU-free days in 28 days
  - Ventilator days
  - Ventilator-free days in 28 days
  - Vasopressor days
  - Vasopressor-free days in 28 days
  - Renal replacement therapy (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 Kidney Disease Improving Global Outcomes [KDIGO] criteria) in patients with abdominal sepsis or NSTI.
- To demonstrate the safety of reltecimod in regard to susceptibility to secondary infections.

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 Stages 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 (ribonucleic acid [RNA] expression) profiling in patients with SA-AKI and compare genomic profiles in patients treated with reltecimod versus placebo.
- To define potential surrogate biomarkers (systemic) that exhibit change from baseline due to treatment with reltecimod.

Methodology:

Study ATB-203 was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study of the safety and efficacy of a 0.5mg/kg dose of reltecimod compared to placebo in the treatment of SA-AKI. Approximately 120 patients were planned to be enrolled in the study and randomly assigned to reltecimod or placebo at a 1:1 ratio.

The primary hypothesis of the study was 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 [calculated using the MDRD formula; from the patient's reference eGFR]) at Day 28 would be higher among reltecimod-treated patients compared to placebo-treated patients.

Randomization was performed at the study center and stratified according to acuity of AKI (i.e., whether or not AKI was diagnosed at the 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 patient age at time of enrolling in the study (≥18 to ≤75 or >75 to ≤85 years old).

Overall, the study was expected to last approximately 36 months (from first patient enrolled to last patient last visit).

Number of Patients (Planned and Analyzed):

A total of 120 patients were planned to be enrolled.

Due to early termination, only 64 patients were randomized in the study (Intent-to-Treat analysis set). Of those, a total of 58 patients were administered the study drug and included in the modified Intent-to-Treat (mITT) analysis set and As Treated (AT)/Safety analysis set (28 patients in the reltecimod group and 30 patients in the placebo group).

Forty-four patients (22 patients in the reltecimod group and 22 patients in the placebo group) subsequently completed the study through Day 29. Five patients each in the reltecimod (17.9%) and placebo (16.7%) groups died prior to Day 29. Reasons for discontinuation of study participation included lost to follow-up (reltecimod, 1 [3.6%]; placebo, 2 [6.7%]) and withdrawal of consent (placebo, 1 [3.3%]). About three-quarters of patients completed the study through Day 90 (reltecimod, 75.0%; placebo, 73.3%), with no deaths in the reltecimod group and 1 additional death in the placebo group between Day 29 and Day 90.

Criteria for Inclusion and Exclusion:

Inclusion criteria:

Patients were included if they were ≥18 to ≤85 years of age with:

- Suspected or confirmed abdominal infection (planned or completed surgical laparotomy or laparoscopy or interventional radiologic procedure for control of underlying abdominal infection within 24 hours of evaluation by medical personnel); or surgically confirmed NSTI.

- Sequential Organ Failure Assessment score ≥2 measured as close as possible to study drug administration (but before study drug was administered).
- Required hospital admission to an ICU or step-down unit (or equivalent).
- Established diagnosis of Stage 2 or 3 AKI (as defined by KDIGO criteria) 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.
- Study medication administered within 6 hours of confirmation of onset of Stage 2 or 3 AKI as established at the study site and decision for surgical or interventional radiology procedure for abdominal infection or confirmed diagnosis of abdominal infection by a surgical or interventional radiology procedure, or after surgical confirmation of NSTI, whichever was later.
- If a female was of childbearing potential, she consistently used an acceptable method of contraception from baseline through Day 28. Non-childbearing potential was defined as current tubal ligation, hysterectomy, or ovariectomy or post-menopause.
- If a male patient's sexual partner was of childbearing potential, the male patient acknowledged that they would consistently use an acceptable method of contraception from baseline through Day 28.
- Signed and dated Informed Consent Form (ICF) by patient or patient's legally authorized representative (LAR).

Exclusion criteria:

- Known prior history of CKD with a documented eGFR <30mL/min by a commonly used formula such as MDRD or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or known GFR <30mL/min. Exception in patients with history of CKD but no available prior eGFR who had documented normal kidney size on ultrasound or computed tomography (CT) evaluation (performed within 90 days of screening).
- Received RRT for CKD: either hemodialysis, peritoneal dialysis, hemofiltration such as continuous veno-venous hemofiltration (CVVH) or hemodiafiltration.
- Documented AKI diagnosis in the last 30 days.
- Documented primary glomerular disease or toxic tubule-interstitial nephritis or other underlying renal diseases significantly affecting renal function at the time of AKI diagnosis.
- Overt peripheral vascular disease in the involved NSTI area or limb amputation considered likely within 7 days due to the peripheral vascular disease.
- Diabetic patients with peripheral vascular disease who presented with below the ankle NSTI.
- Inability to maintain a mean arterial pressure >50mm Hg and/or systolic blood pressure >70mm Hg for at least 1 hour prior to administration or respiratory failure such that an SaO_2 of 80% could not be maintained for at least 1 hour prior to administration or refractory coagulopathy (international normalized ratio [INR] >5) or thrombocytopenia (platelet count <20,000) for at least 1 hour prior to administration.
- Severe neurological impairment due to cerebrovascular accident or cardiac arrest.
- Recent cerebrovascular accident in the last 3 months.
- Cardiac arrest requiring cardiopulmonary resuscitation within the past 30 days.
- Not expected to survive throughout 28 days due to an underlying medical condition.
- Classified as "Do Not Resuscitate" or "Do Not Treat" or the patient's family was not committed to aggressive management of the patient's condition.

- Any concurrent medical conditions, which in the opinion of the Investigator, could compromise the safety of the patient or the objectives of the study or the patient would not benefit from treatment such as: congestive heart failure (New York Heart Association [NYHA] Class III to IV; very severe chronic obstructive pulmonary disease (Global Initiative on Chronic Obstructive Lung Disease [GOLD] Stage IV or continuous home oxygen); liver dysfunction (Child-Pugh Class C), primary or acquired immunodeficiency or immunosuppression due to treatment with 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 underlying infection; receiving or about to receive chemotherapy or biologic anti-cancer treatment (hormonal manipulation therapies for breast and prostate malignancies permitted); hematologic or lymphatic malignancies in the last 5 years.
- Burn wounds comprising >20% of body surface area.
- Acute pancreatitis with no established source of infection, uncomplicated appendicitis, cholangitis, or cholecystitis (necrotic or gangrenous gallbladder or appendix with peritonitis was allowed).
- Pregnant or breastfeeding women; women of childbearing potential were mandated to have a negative β-subunit human chorionic gonadotropin (hCG) pregnancy test immediately prior to study entry.
- Previous enrollment in a clinical study 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.
- Previous enrollment in any reltecimod protocol (ATB-001, ATB-201, ATB-202, or ATB-203).
- Patients under guardianship or trusteeship (France only).
- Absence of social insurance (France only).

Test Product, Dose and Mode of Administration, Batch Number:

Reltecimod is the sodium salt of a 10 amino acids synthetic peptide that is homologous to specific amino acid residues of the T-lymphocyte receptor CD28.
Reltecimod was supplied in glass vials as a lyophilized powder to be reconstituted with sterile water for injection (WFI). The study drug was reconstituted on the day of its administration, in close proximity to infusion time, and several vials were pooled to achieve the weight-based dose. Final volume for infusion was calculated based on the patient's weight plus adequate priming volume of the IV line.
The study drug was administered as an IV infusion, separate from other medications, over 10 minutes using a syringe pump (manually pushed if approved by the Medical Monitor).
The dose of reltecimod was 0.5mg/kg, administered as a single dose, either during or immediately after the first surgery; the study drug was only administered after NSTI diagnosis was confirmed surgically. The study personnel, clinical staff, and patients remained blinded to study drug treatment. Only the assigned study pharmacist or authorized qualified designate preparing the drug was unblinded to the treatment.

Batch number: 2439-102

Reference Therapy, Dose and Mode of Administration, Batch Number:

Blinded placebo was sterile normal saline (0.9%), provided by the study centers, volume calculated similarly as for the active group according to the patient's weight, plus adequate priming volume of the IV line.

Batch number: Not applicable, supplied by study centers

Duration of Treatment:

The study drug was administrated as a single IV infusion over 10 minutes.

Criteria for Evaluation/Endpoints:

Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study was freedom from durable loss of renal function at Day 28. The primary effectiveness endpoint was defined by all of the following:

- Alive at Day 28,
- Free of dialysis at Day 28, and
- Less than a 37% loss of eGFR (measured with the MDRD formula from the patient's reference eGFR) at Day 28.

Reference creatinine values, baseline AKI stage and percentage loss of eGFR at Day 28 were determined algorithmically. Percentage loss of eGFR determined algorithmically was based on a comparison of eGFR at Day 28 compared to an algorithmically determined reference creatinine value.

Note: The protocol allowed patients to qualify for enrollment in terms of AKI stage based on urine output.

Secondary Effectiveness Endpoints

The secondary effectiveness endpoints for this study were:

- Freedom from durable loss of renal function at Day 14
- Freedom from durable loss of renal function at Day 90

Reference creatinine values, baseline AKI stage and percentage loss of eGFR at Days 14 and 90 were determined algorithmically. Percentage loss of eGFR determined algorithmically was based on a comparison of eGFR at Day 28 compared to an algorithmically determined reference creatinine value.

- Resolution of organ dysfunction (organ resolution was defined as having a total mSOFA score of ≤1) at Day 14
- Resolution of specific organ dysfunction (defined as having an individual organ mSOFA score of ≤1) at Day 14
- Critical care and hospital stay parameters
  - Hospital LOS
  - ICU LOS
  - ICU-free days in 28 days
  - Days on ventilator
  - Ventilator-free days in 28 days
  - Vasopressor days
  - Vasopressor-free days in 28 days
  - Discharge status
- Patient survival at Days 14, 28, and 90
- Presentation of Stages 1, 2, or 3 AKI (using the KDIGO criteria)
- Stratifications involving Day 14 mSOFA ≤1 versus Day 14 mSOFA ≥2
  - Compare critical care parameters between Day 14 mSOFA ≤1 and Day 14 mSOFA ≥2
  - Compare critical care parameters between treatment groups in those with Day 14 mSOFA ≤1
  - Compare critical care parameters between treatment groups in those with Day 14 mSOFA ≥2
- Among patients presenting with cardiovascular failure (shock), evaluate treatment group predicting Day 14 mSOFA ≤1

- Survival to Day 90 as a function of freedom from durable loss of renal function at Day 28 (overall and by treatment group)

Exploratory Effectiveness Endpoints

The following were exploratory endpoints for this study:

- Improvement or freedom from durable loss of renal function at Day 14
- Improvement or freedom from durable loss of renal function at Day 28
- Improvement or freedom from durable loss of renal function at Day 90
- Incidence of CKD at Day 90 as determined by detection of albuminuria and eGFR using CKD-EPI equation
- Urinary albumin/creatinine ratio will be summarized for measurements made at screening, Day 1, Day 3, Day 7, Day 14, Day 29, and Month 3. The measure was used to assess kidney injury and was a marker of CKD.
- C-reactive protein was summarized for measurements made at screening, Day 7, Day 14, and Day 29, and for changes from screening to Day 7, Day 14, and Day 29.
- Evaluation of RRT use (i.e., type of RRT)

Safety Endpoints

The following were safety endpoints for this study:

- Adverse events (AEs)
- Clinical parameters (heart rate, blood pressure, vital signs)
- Laboratory parameters (clinical chemistry and hematology)
- Survival

Statistical Methods:

Primary Efficacy Analysis

The primary efficacy comparison involved testing the following one-sided superiority hypotheses:
Ho: $\pi_{0.50} - \pi_{placebo} \leq 0$ **versus Ha:** $\pi_{0.50} - \pi_{placebo} > 0$; where $\pi_{0.50}$ and $\pi_{placebo}$ represented 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 patients 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 α=0.025. The null hypothesis will only be rejected if the proportion of responders is larger in the active drug group compared to placebo.

Sample Size Justification

This study was designed to enroll 120 subjects randomized in a 1:1 ratio to either reltecimod 0.5mg/kg (n=60) or placebo (n=60), both in addition to SoC. Sample size analysis was performed assuming all patients would be evaluable for the primary endpoint due to using last observation carried forward (LOCF) for patients missing the creatinine value on Day 28. The primary efficacy hypothesis was tested using an unadjusted $\chi 2$ statistic with a one-sided α=0.025 significance level. Rejection of the null hypothesis would 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.

Secondary Efficacy Analysis

The same analysis was performed for freedom from durable loss of renal function at Days 14 and 90 and for improvement in freedom from durable loss of renal function at Days 14, 28, and 90.

Additional secondary endpoints included mSOFA over time, critical care and hospital stay parameters (ICU and ICU-free days, ventilator days and -free days, vasopressor days and -free days, and hospital LOS). Analyses for these endpoints were generally descriptive, with emphasis on characterizing clinical effect sizes. Nominal p-values were presented. Categorical outcomes were described using counts and percentages with nominal p-values determined through chi-square or exact methods. Critical care and hospital stay endpoints were described using nonparametric approaches including 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 were used for time-to-recovery endpoints.

Safety Analysis

The primary safety measures were AEs (including serious adverse events [SAEs]), deaths, clinical safety laboratory results, physical examination (PE) results, vital signs, and survival through Day 29. For the purpose of this study, death was captured as a clinical outcome and only recorded as an SAE if deemed related to the study drug.

The safety profiles were 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 were summarized by mean changes over time using descriptive statistics (sample size [N], mean, standard deviation [SD], median, minimum, and maximum). The presence of clinically significant safety findings was summarized by shift tables separately for each group using counts and percentages. Adverse events were classified according to system organ class (SOC) and preferred term (PT) and summarized by counts and percentages separately for those recorded on Day 0 (prior to study drug administration) and those with onset on Day 1 or later. Adverse events were summarized by relationship to the study drug, severity, and whether they were serious. Specific summaries involved AEs and SAEs in the Infection/Infestation SOC. Vital signs (temperature, systolic BP, diastolic BP, respiration rate, and heart rate) and weight were summarized across time (Days 0, 1, 2, 3, 7, 10, 14, 21, and 29) and separately by treatment group by N, Mean, and SD.

Analysis Sets

The following analysis sets are referred to in this study report (only data from the As Treated/Safety and mITT) sets are discussed in this study report:

- Intent-to-treat (ITT): The ITT analysis set included all randomized patients.
- As Treated (AT): The AT/Safety analysis set included all randomized patients who were exposed to study medication (active or placebo). The AT/Safety analysis set was used in primary safety analyses with patients assigned to actual treatment received and in supporting effectiveness analyses.
- Modified Intent-to-treat (mITT): The mITT analysis set included patients who were exposed to study medication and who had a definitive diagnosis of abdominal sepsis or NSTI and Stage 2 or Stage 3 AKI with patients assigned to the treatment actually received. The mITT analysis set may be used in supporting effectiveness analyses if more than a small number of such exclusions were made or more than a small number of patients were not treated with their randomly assigned treatment allocation.
- Per Protocol (PP): Optionally, a PP analysis set was used in secondary effectiveness analyses. The PP analysis set included patients in the mITT analysis set assigned according to actual treatment received and excluded patients with either: 1) significant violations of inclusion or exclusion criteria with potential to confound treatment effect estimates, or 2) post randomization protocol violations with potential to confound treatment effect estimates. Exclusions from the PP analysis set were determined based on blinded clinical data. The PP analysis may have been further restricted to exclude patients who did not survive at 3 least days when evaluating critical care variables.

Summary – Conclusions:

Disposition

ATB-203 included 28 patients who received reltecimod 0.5mg/kg and 30 patients who received placebo and were included in the mITT analysis set. As no patients were excluded from the mITT analysis set, the mITT and As Treated/Safety analysis sets are identical. Of the 58 patients in the As Treated/Safety analysis set, 22 (78.6%) of 28 patients in the reltecimod group and 22 (73.3%) of 30 patients in the placebo group completed the study through Day 29. Five patients in each of the reltecimod (17.9%) and placebo (16.7%) groups died prior to the Day 29 visit. Reasons for discontinuation before Day 29 included 1 patient in the reltecimod group and 2 patients in the placebo group that were lost to follow-up, and 1 patient in the placebo group who withdrew consent. About three-quarters of patients completed the study through Day 90 (reltecimod, 75.0%; placebo, 73.3%), with no deaths in the reltecimod group and 1 death in the placebo group between Day 29 and Day 90. The number of patients in each group in the different analysis sets are provided in the following table.

	Total	**Reltecimod 0.5mg/kg**	**Placebo**
Analysis Sets	**N**	**n**	**n**
Intent-to-treat	64	29	35
As Treated/Safety	58	28	30
Modified Intent-to-treat	58	28	30
Per Protocol	52	26	26

Demography and Baseline Characteristics:

In the As Treated/Safety analysis set, demographics and baseline characteristics were well-balanced between the reltecimod and placebo groups. The mean age for all subjects was 61.7 years (range: 21 to 85 years). Approximately half of the patients were female (53.4%), White (77.6%), and not Hispanic or Latino (89.7%). Mean (SD) body mass index (BMI) was 31.4 (9.9) kg/m^2 at baseline; this was 30.5 (6.9) kg/m^2 and 32.3 (12.2) kg/m^2 in the reltecimod and placebo groups, respectively.

Most patients had abdominal infection (96.6%) as the cause of sepsis as NSTI was only added approximately 2 months prior to the end of the study. Approximately one third (29.3%) of patients had diabetes mellitus and 22.4% had cardiovascular disease; 10.3% were smokers and 5.2% admitted to alcohol abuse. Overall, a higher number of patients had diabetes mellitus in the reltecimod group, and more patients were smokers in the placebo group. Mean baseline mSOFA scores were well-balanced (reltecimod, 4.9; placebo, 5.4), reflecting comparable baseline organ dysfunction/failure, and the mean baseline APACHE II scores were similar (reltecimod, 17.1; placebo, 16.4). A slightly higher number of patients presented with cardiovascular failure in the placebo group (reltecimod, 42.9%; placebo, 56.7%), while a similar percentage of patients presented with respiratory failure (reltecimod, 7.1%; placebo, 10.0%). A higher number of patients presented with Stage 2 AKI in the placebo group (reltecimod, 71.4%; placebo, 83.3%), while more patients presenting with Stage 3 AKI in the reltecimod group (reltecimod, 28.6%; placebo, 16.7%). A higher number of patients were diagnosed with AKI at the time of diagnosis of infection in the reltecimod group (reltecimod, 60.7%; placebo, 40%). A higher number of patients were diagnosed with AKI by serum creatinine (reltecimod, 64.3%, placebo, 50.0%) than diagnosed by urine output (reltecimod, 35.7%; placebo, 46.7%). Most of the patients had a reference pre-infection serum creatinine value(s) within the past year (reltecimod, 71.4%; placebo, 73.3%).

The pathogen types most commonly isolated from tissue cultures were Gram-negative only (30.3%), followed by Mixed Gram-positive and -negative (21.2%), and Mixed Gram-positive and negative and anaerobes (15.2%). Types of pathogens were generally balanced between the treatment groups.

Efficacy Results:

As the study was terminated early, conclusions regarding efficacy are limited. The key efficacy findings from ATB-203 were as follows:

- The primary efficacy analysis did not show a statistically significant difference between the reltecimod and placebo groups in freedom from durable loss of renal function at Day 28 (reltecimod, 71.4%; placebo, 76.7%). Secondary efficacy analysis also did not show a statistically significant difference in freedom from durable loss of renal function at Day 14 or Day 90 or freedom or improvement from durable loss of renal function at Day 14, Day 28, or Day 90.
- Evaluation of the observed values and LOCF results revealed no statistically significant differences in the total mSOFA score or total SOFA score, or organ specific scores between the reltecimod and placebo groups.
- Health care resource utilization (HCRU) showed clinically meaningful, although not statistically significant, trends favoring reltecimod over placebo. ICU-free days and ventilator-free days were approximately 1 day more in the reltecimod group, while ICU days and ventilator days were approximately 1 day less in the reltecimod group. Hospital days were 3.8 days less in the reltecimod group.
- Discharge status regarding functional outcomes (i.e., home or rehabilitation facility versus skilled nursing/long-term care, transfer to another acute care hospital or inpatient death) favored reltecimod over placebo, especially regarding patients discharged to home.
- Resolution of organ dysfunction/failure (Day 14 mSOFA $\leq$1) was strongly associated with several clinically meaningful outcomes including the following:
  - Higher survival between Day 14 and Day 90
  - The number of ICU days, ventilator days, vasopressor days, and hospital days were markedly improved based on organ dysfunction/failure resolution.
  - Discharge to a more favorable location with statistically significantly more patients discharged to home
- Differences in mortality and CKD could not be determined due to the low incidence of mortality in the study.

Safety Results:

Under the conditions of this study, reltecimod was well-tolerated, with a safety profile similar to that observed with placebo.

- The profile and incidence of TEAEs were 50.0% in the reltecimod group and 73.3% in the placebo group with no TEAEs considered by the Investigator to be related to reltecimod and no discontinuations from the study or from study drug due to a TEAE.
- Severe TEAEs were evenly distributed between the reltecimod (32.1%) and placebo groups (30.0%).
- Serious TEAEs were reported in 32.1% of patients in the reltecimod group and 30.0% of patients in the placebo group. There were no serious TEAEs by PT that occurred in more than 1 reltecimod patient.
- No signal for immunosuppression was observed either in TEAEs of special interest (i.e., Infections and infestations SOC) or hematology (i.e., lymphocyte laboratory data).
- No clinically relevant trends were observed in hematology parameters with respect to observed values and changes from baseline to Day 1, 3, 7, 14, or 29.
- No clinically relevant trends were observed in clinical chemistry parameters with respect to observed values and changes from baseline to Day 7 or Day 14. There were no events of drug-induced liver disease.

- No clinically relevant trends were observed in vital signs with respect to observed value and changes from baseline through Day 29.

Conclusions:

The primary efficacy endpoint evaluating freedom from durable loss of renal function, in the setting of SA-AKI, was not met. Reltecimod did show a clinically meaningful, but not statistically significant, improvement in HCRU and discharge status. Resolution of organ dysfunction/failure by Day 14 (as measured by mSOFA ≤1) showed a highly statistically significant effect on HCRU. Reltecimod was well-tolerated in this study, and the study data further support the safety of reltecimod in a critically ill population.

Date and Version of Report:

06 August 2020, Version 1