



Atox Bio Announces a Positive Effect of Reltecimod on Resolution of Organ Dysfunction in Phase 3 ACCUTE Trial for Patients with Necrotizing Soft Tissue Infection (“Flesh Eating Disease”)

- After Discussions with FDA, NDA Submission Planned for 3Q 2020 under Accelerated Approval Pathway -

- Reltecimod in conjunction with currently available standard of care demonstrated a significant difference in the percentage of patients who achieved resolution of organ dysfunction/failure by Day 14 versus standard of care alone
- Resolution of organ dysfunction/failure at Day 14 is associated with improved survival at Day 90
- Treatment effects in composite NICCE primary endpoint were significant in the clinically evaluable population analysis but not in the primary mITT analysis
- Patients receiving reltecimod demonstrated improvement in hospital discharge status versus placebo
- Patients presenting with shock appeared to particularly benefit
- Reltecimod was well tolerated
- Peer reviewed results published in latest electronic edition of Annals of Surgery

Durham, NC and Ness Ziona, Israel –July 10, 2020 – [Atox Bio](#) today announced results from the randomized, double-blind, placebo-controlled Phase 3 ACCUTE (A_B103 C_linical C_omposite endpoint S_tU_dy in Necrotizing Soft T_issue infE_ctions) trial of reltecimod for the early treatment of severe Necrotizing Soft Tissue Infection (NSTI). The data showed a significant difference in the percentage of patients administered reltecimod who achieved resolution of organ dysfunction/failure by Day 14 vs. the percentage of patients who received placebo. Resolution of organ dysfunction by day 14 has been noted in the literature and was shown in this trial to have a beneficial effect on 90-day mortality. As this was the first pivotal study ever performed in NSTI, a necrotizing infection clinical composite endpoint (NICCE) was developed. This endpoint was designed to assess both the local and systemic components of NSTI and included the measurement of resolution of organ dysfunction/failure. While statistical significance on the primary composite endpoint was not achieved in the modified intent to treat (mITT) population, the efficacy assessment in the clinically evaluable (CE) population demonstrated a p-value=0.039. Atox Bio believes that, for the reasons detailed below, the CE population reflects the more clinically relevant and statistically appropriate patient population for evaluation of the treatment effect of reltecimod. Atox has reviewed the topline results of this trial with the US Food & Drug Administration (FDA) and, based on these discussions, plans to submit a New Drug Application (NDA) to the FDA in Q3 2020 under the Accelerated Approval Pathway with resolution of organ dysfunction being the basis for this approval pathway.

"Patients with NSTI are critically ill and could greatly benefit from a treatment option designed specifically for their condition," said Eileen Bulger, M.D., Chief of Trauma at Harborview Medical Center, Professor of Surgery at the University of Washington, and Principal Investigator for the ACCUTE trial. "Reltecimod has the potential to significantly advance the standard of care for NSTI by addressing a major unmet medical need for these complex and challenging patients and appears to be well tolerated."

"Successful completion of the ACCUTE trial is a major milestone for Atox Bio that reinforces our commitment to patients with NSTI. This is a potentially life-threatening condition with significant morbidity and long-term mortality that has no FDA-approved treatment." said Dan Teleman, CEO of Atox Bio. "Reltecimod has been designed to modulate rather than completely suppress acute inflammation that can lead to a dysregulated immune response and we are actively working to bring this important new potential therapy to patients."

About the Study

As the first pivotal study ever performed in NSTI, a new clinical composite responder analysis was developed as the primary endpoint. The necrotizing infection clinical composite endpoint (NICCE) that was developed was designed to assess both the local and systemic components of NSTI. NICCE included a Modified Sequential Organ Failure Assessment (mSOFA) scoring tool to evaluate resolution of organ dysfunction. SOFA scores have been shown in previous studies to be a good indicator of prognosis in other septic conditions. All patients allowed into the study had to have significant organ dysfunction in one or more organs at baseline and the measure of resolution of organ dysfunction using mSOFA was consistent with SEPSIS-3 definitions.

Elevated mSOFA at Day 14, defined as mSOFA >1, delineates persistent organ dysfunction in which a patient could require prolonged ventilation, ongoing blood pressure support and dialysis or other interventions for complications of acute kidney injury at a time point that has been associated with the development of chronic critical illness.^{1,2} At the Day 14 time point, mSOFA offers a simple categorical tool to help distinguish patients at risk for persistent organ dysfunction that is associated with longer term morbidity and mortality.

Blinded study drug (reltecimod or saline placebo) was administered by a single 10-minute infusion. All patients received currently available standard of care, which includes surgical debridement, broad spectrum antibiotics and supportive intensive care. Organ dysfunction and failure can progress rapidly in these patients and intervening as early as possible once organ dysfunction has begun is considered critical for any immune-based therapy. For this reason, patients were required to be administered the blinded study drug within 6 hours of being scheduled for surgery to confirm the NSTI diagnosis, often before all of a patient's clinical information is available.

While analysis of the mITT population was the primary analysis, the CE population, in which only those patients who met the appropriate study entry criteria were included, was considered relevant in this study because of the potential to inadvertently enroll patients with unrelated chronic organ conditions that could not be cured by an acute treatment for NSTI and thus could

confound estimates of treatment effects. For this reason, Atox Bio considers the CE population the more clinically relevant and statistically appropriate analysis population. Of the 290 patients enrolled in the study, 13 were excluded from the CE analysis population for failure to meet pre-defined study entry criteria. All exclusions were identified programmatically from the study database and reviewed by blinded medical and statistical reviewers prior to unblinding the trial.

Results

Results of the study demonstrated that, in the analysis of the mITT population on the NICCE primary endpoint, 48.6% of patients achieved clinical success on relteceimod vs. a 39.9% success rate in patients on placebo. This result did not achieve statistical significance ($p=0.14$). Given the consequences of persistent organ dysfunction, a key outcome of the study was the assessment of resolution of organ dysfunction, defined as Day 14 mSOFA ≤ 1 in combination with a decline of at least 3 mSOFA points from baseline. In this assessment, relteceimod demonstrated a distinct advantage over placebo (65.1% success vs. 52.6%, $p=0.041$).

Using the more clinically relevant patient population in the CE analysis, 52.6% of patients receiving relteceimod achieved clinical success on the NICCE primary endpoint vs. 40.3% on placebo ($p=0.039$). In the evaluation of resolution of organ dysfunction, as described above, relteceimod demonstrated a strong clinically meaningful effect over patients receiving standard of care alone, with 70.9% of patients on relteceimod achieving resolution of organ dysfunction by Day 14 vs. 53.4% on placebo ($p=0.005$).

There is increasing evidence that resolving organ dysfunction by Day 14 in septic patients such as those enrolled in this trial has important benefits. Studies have shown that patients who remain chronically critically ill with organ dysfunction beyond 14 days are more likely to require long-term care, develop recurrent infections and have an increased risk of late mortality, after day 28, and poor functional recovery.

Consistent with these findings, in this study in patients who survived to Day 14, whether on relteceimod or placebo, those that had resolved organ dysfunction by Day 14 had a 90-day mortality of 2.4% vs. 21.5% in patients who had persistent organ dysfunction at Day 14 ($p<0.001$) in the CE analysis population. While not showing a difference in mortality at Day 28 and although not powered to show significance for mortality generally, in those patients surviving to Day 14, the Day 14 to Day 90 mortality was 5.9% on relteceimod vs. 11.5% on placebo ($p=0.12$) in the CE analysis population. In the mITT analysis, the Day 14 to Day 90 mortality was 6.5% on relteceimod vs. 11.2% on placebo ($p=0.17$).

Additional pre-specified secondary endpoints were evaluated and of these evaluations, patients presenting with shock and hospital discharge status demonstrated clinically relevant effects that may lead to improved patient outcomes. In the subgroup of patients that entered the study with septic shock, requiring vasopressors prior to dosing, 72.5% on relteceimod successfully resolved organ dysfunction by Day 14 vs. 49.1% on placebo ($p=0.008$) in the mITT analysis. In the CE analysis population, the results were 75.1% on relteceimod vs. 49.1% on placebo ($p=0.003$) achieving resolution of organ dysfunction by Day 14.

Patients on reltecimod also showed benefit in the percentage of those with a favorable hospital discharge status in this trial. Favorable discharge status was defined as being either sent home or to a rehabilitation facility. Unfavorable discharge status was defined as being discharged to a skilled nursing facility, other acute care hospital or dying before discharge. In patients surviving to Day 14, those on reltecimod had a clinically beneficial improvement in favorable hospital discharge status in the CE analysis population (68.6% on reltecimod vs. 54.6% on placebo, $p=0.024$). In the mITT analysis, 60.6% on reltecimod had favorable discharge status and 50.0% placebo had favorable discharge status ($p=0.071$).

Reltecimod was well tolerated in this study, with the profiles of adverse events being similar between the reltecimod and placebo treatment groups. The most common adverse events (~5%) reported in patients treated with reltecimod were anemia (reltecimod 6.3%, placebo 4.8%), acute kidney injury (reltecimod 5.6%, placebo 5.4%), atrial fibrillation (reltecimod 4.9%, placebo 6.8%), and peripheral edema (reltecimod 4.9%, placebo 1.4%).

Serious adverse events occurred in 20.3% of patients receiving reltecimod and 17.0% of patients receiving placebo. The most common serious adverse events were atrial fibrillation (reltecimod 2 [1.4%], placebo 4 [2.7%]), acute myocardial infarction (reltecimod 2 [1.4%], placebo 3 [2.0%]), acute respiratory distress syndrome (reltecimod 2 [1.4%], placebo 3 [2.0%]), and pulseless electrical activity (reltecimod 3 [2.1%], placebo 2 [1.5%]).

There was no apparent difference in secondary infections between reltecimod and placebo treated arms in this study, which is important in this fragile patient population.

The [ACCUTE pivotal study](#) manuscript is now available from the Annals of Surgery as an ePublication entitled, “A Novel Immune Modulator for Patients with Necrotizing Soft Tissue Infections (NSTI): Results of a Multicenter, Phase 3 Randomized Controlled Trial of Reltecimod (AB 103).”

About Reltecimod

Reltecimod is a synthetic peptide antagonist of both superantigen exotoxins and the CD28 T-cell costimulatory receptor.³ By modulating, but not inhibiting, the body’s acute inflammatory response, reltecimod is designed to help control the cytokine storm that could otherwise quickly lead to morbidity and mortality. FDA granted reltecimod Fast Track status and orphan drug designation for NSTI. The European Commission granted orphan designation for reltecimod in the treatment of NSTI.

About Necrotizing Soft Tissue Infections (NSTI)

NSTI, commonly referred to as “flesh eating disease or bacteria,” is a serious infection that can travel quickly from the infection site and requires frequent, rapid surgical intervention to remove dead and infected tissue to stop further progression and the need for amputation. By their nature, these surgeries often leave patients significantly disfigured. In more serious cases, acute inflammation that results from this infection leads to systemic organ dysfunction in the heart,

lungs and/or kidneys. Even with the best current standard of care which includes surgical debridement, broad spectrum antibiotics and supportive intensive care, multi-organ failure frequently occurs. Mortality rates are significant in both the short and intermediate term, and patients who do survive often face long and expensive hospital and rehabilitation center stays. Hospital discharge data indicates there are approximately 30,000 cases of NSTI in the US each year, with a similar number in Europe, and there are currently no therapies approved for this indication.

About ACCUTE

ACCUTE (AB103 Clinical Composite endpoint Study in Necrotizing Soft Tissue infections) is a Phase 3 randomized, placebo-controlled study that enrolled 290 patients across sites in the US and France. It evaluated the safety and efficacy of a single dose of intravenous reltecedimod 0.5mg/kg versus placebo (0.9% saline) administered in conjunction with surgical debridement (removal of damaged skin, subcutaneous tissue, fascia, and sometimes muscle), antibiotic therapy, and supportive care in patients ≥ 12 years of age with NSTI. The trial also assessed hospital discharge status and impact on healthcare resource utilization.

About Atox Bio

Atox Bio is a late stage clinical company that develops immunotherapies for critically ill patients. The ACCUTE study was funded in whole or in part with Federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority (BARDA), under Contract No. HHSO100201400013C. Major investors in the company include SR One, OrbiMed, Lundbeckfonden Ventures, Arix Bioscience plc and Adams Street Partners. The Company was established by Prof. Raymond Kaempfer and Dr. Gila Arad from the Hebrew University of Jerusalem and Yissum. Please visit www.AtoxBio.com for more information.

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Media Contact:

Julia Wilson

JW Communications

juliawilsonuk@gmail.com

+44 781 8430877

¹ Gardner AK, Ghita GL, Wang Z, et al. The Development of Chronic Critical Illness Determines Physical Function, Quality of Life, and Long-Term Survival Among Early Survivors of Sepsis in Surgical ICUs. Crit Care Med. 2019;47(4):566–573.

² Brakenridge SC, Efron PA, Cox MC, et al. Current epidemiology of surgical sepsis: discordance between inpatient mortality and 1-year outcomes. Ann Surg. 2019 Sep 1;270(3):502-10.

³ Shirvan, A., Bulger, E., and Dankner, W. Reltecedimod. Drugs of the Future 2018, 43(4): 243-259.