COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Threat Agnostic And Host-directed Therapeutic AV-001 To Treat Vascular Dysfunction: Randomized, Double-blind, Placebo-controlled Phase 1 Single And Multiple-dose First-in-human Study In Healthy Subjects For The Treatment Of Acute Respiratory Distress Syndrome

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Background: Acute respiratory distress syndrome (ARDS) is a clinical condition of great significance to the military, known to arise from traumatic injuries sustained during active Service. Thermal injuries and inhalation of weaponized biological or chemical agents pose a significant risk to warfighters and civilian targets, leading to pulmonary toxicity, vascular dysfunction, and potentially ARDS. Purpose: Currently there are no approved therapeutics to treat ARDS or to prevent its onset, indicating a clear unmet medical need. Objective: Vasomune Therapeutics Inc. is developing AV-001, a fully synthetic PEGylated tetrameric peptide ligand to the Tie2 receptor, as a threat agnostic therapeutic for ARDS. Rationale: The activation of the Tie2 signaling cascade is critical for maintaining endothelial barrier function. We have demonstrated that AV-001 reduces vascular leak and promotes survival in a model of lethal influenza, independent of viral strain. This abstract describes the completed Phase 1 single and multiple ascending dose (SAD and MAD) first-in-human findings. Relationship to other areas: As a threat agnostic, host defense therapeutic AV-001 has demonstrated pre-clinical efficacy across multiple indications such as hemorrhagic shock, wound healing, radiation-induced burns, and cerebrovascular injury. Methods: In the SAD phase, healthy subjects were divided into cohorts receiving AV-001 or placebo, with a post-dose follow-up and an end-of-study visit. The MAD phase had subjects take daily doses for 7 days, with similar follow-up. Sample collection for pharmacokinetic (PK) and pharmacodynamic (PD) analysis were taken. Safety endpoints included adverse events, clinical labs, vital signs, ECG, and physical examinations.Results: AV-001 Injection demonstrated linear PK over the dose range studied. Geometric mean plasma AV-001 concentrations, Cmax, and AUC all increased in a dose-related manner over the dose range of 1.4 µg/kg, 5.6 µg/kg, 18 µg/kg, and 56 µg/kg. The t1/2 of 2.19 hours at the SAD dose of 56 µg/kg is representative of the actual half-life. Exposure to AV-001 was similar on day 1 versus day 7 following once daily dosing of AV-001 1.4 µg/kg/day and 56 µg/kg/day for 7 consecutive days. The PD of AV-001 Injection on Tie2-expressing leucocytes (TELs) demonstrated on-target Tie2 activation. AV-001 Injection was safe and well-tolerated at all doses when delivered for 7 consecutive days. There were no deaths, no discontinuations, no severe adverse events, no suspected unexpected severe adverse reactions, no adverse events of special interest, no clinically significant abnormal laboratory values, abnormal ECGs, or hypotension characteristics (i.e., sustained decreases in systolic blood pressure and compensatory increases in heart rate). Conclusions: AV-001 Injection was safe and well-tolerated at all doses in both SAD and MAD studies. AV-001 Injection demonstrated linear PK over the dose range studied. The PD of AV-001 Injection demonstrated on-target effects on TELs. Phase 2a studies are currently ongoing. Impact to the JSTO mission and the Joint Force: As a medical countermeasure (MCM), our pre-clinical work points to AV-001 as a threat agnostic, host-directed therapeutic to treat endothelial dysfunction. Clinically, AV-001 has an excellent safety and tolerability profile making it a strong candidate for further development as a MCM for the warfighter and for national preparedness.

Vasomune acknowledges the support of The Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense, in the amount of $2,821,652 through the Peer Reviewed Medical Research Program under Award Number W81XWH-20-1-0558 for support of IND enabling research. Opinions, interpretations, conclusions, and recommendations are those of the author(s) and are not necessarily endorsed by The Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense. Vasomune acknowledges the support of National Research Council Canada IRAP Award #965762 for support of Phase 1 study, AV-001-PK-001. Vasomune acknowledges the on-going financial and technical support provided by AnGes, Inc.