Background AgenT-797 is a novel allogeneic iNKT cell therapy demonstrating activity in malignances and serious viral infections (i.e., SARS-CoV-2). In response to inflammatory injury, iNKTs home to critical organs, including lungs, dampen proinflammatory cytokines and protect epithelial tissues. iNKTs drive response through activation of innate and adaptive immunity, recruitment/trans-activation of NK, B, and T cells, and myeloid cells via contact and soluble mediators. iNKTs represent a novel and attractive potential immunotherapy for viral ARDS. This analysis presents results from an ongoing phase 1/2 study of agenT-797 in mechanically ventilated patients with moderate to severe ARDS secondary to COVID-19; NCT04582201.

Methods As of February 2022, patients on mechanical ventilation with confirmed moderate to severe (Berlin Definition) ARDS, secondary to COVID-19 were treated with a single infusion of agenT-797 at 100, 300, or 1000 x 10^6 iNKT cells. Primary endpoint was safety and secondarily, time to extubation, prevention of secondary infections, persistence and alloimmunity were evaluated. Clinical benefit was defined as improvement/resolution of viral ARDS evaluated as time to extubation and survival at 30 days post-infusion.

Results Twenty evaluable patients were treated with agenT-797 with a median age of 66 years (range 26-77; 85% ≥65). Patients enrolled early in pandemic (pre-vaccines) and were heavily pre-treated with remdesivir, steroids and/or tocilizumab. No dose-limiting toxicities were observed. Tolerability was favorable with no cytokine release syndrome (CRS), neurotoxicity, or severe immune-related AEs. One SAE was deemed possibly related to agenT-797 (Dyspnea, Grade 4). The most frequent AEs deemed possibly related was pyrexia (grade 1; n=6). Survival was 70% (14/20) in this predominantly elderly, mechanically ventilated population. Early signals of reduction in ARDS symptoms, rapid extubation, and reduction in secondary infections were observed.

AgenT-797 was detected in peripheral blood up to day 6 post-infusion, consistent with a rapid translocation from blood to tissue. Spikes in the blood during D1 and D2 showed a dose-proportional relationship, however, increased dose did not lead to prolonged peripheral persistence. Additional translational and biomarker evaluation is underway.

Conclusions In patients with severe viral ARDS secondary to SARS-CoV-2, agenT-797 demonstrated encouraging survival and disease mitigating benefit with a favorable tolerability profile. The deep and broad activity observed is likely attributed to iNKT cells’ ability to promote viral clearance, home to the lungs, and reduce inflammation. These findings support the potential for a variant-agnostic therapy for patients with viral ARDS, a condition for which there are currently no effective therapies.

Trial Registration NCT04582201