Background AU-007 is a computationally designed mAb that binds IL-2 on its CD25 binding epitope. AU-007 bound IL-2 (A/IL-2) cannot bind to trimeric (CD25, CD122, CD132) IL-2 receptors (IL-2R) on Tregs, vascular endothelium, or eosinophils, but IL-2’s binding to dimeric IL-2Rs (CD122, CD132) on T effector and NK cells is unhindered. AU-007 thus redirects IL-2 towards T effector and NK cell activation, while diminishing Treg activation and vascular leak. Unique among IL-2 therapeutics, AU-007 redirects IL-2 generated from T effector cell expansion, converting a Treg-mediated autoinhibitory loop into an immune stimulating loop.

Methods This Phase 1 study (NCT05267626) consists of 3 dose escalation arms. Arm 1A evaluates escalating doses of AU-007 (intravenous, every 2 weeks [Q2W]). Arm 1B evaluates AU-007 (Q2W) plus one low-dose aldesleukin subcutaneous injection. The AU-007 dose is fixed with escalating aldesleukin doses in sequential cohorts. Arm 1C evaluates AU-007 plus escalating doses of concomitant low-dose subcutaneous aldesleukin, both Q2W. Tumor assessments occur with each 8-week cycle.

Results As of 15 June 2023, 24 patients have received AU-007 +/- aldesleukin, 13 in Arm 1A, 6 in Arm 1B, and 5 in Arm 1C. AU-007 (+/- aldesleukin) was well-tolerated, with no DLTs, at doses up to 9 mg/kg of AU-007 alone, 4.5 mg/kg + one 45,000 IU/kg aldesleukin dose, and 4.5 mg/kg + 15,000 IU/kg aldesleukin Q2W. Two patients had transient lymphopenia (Grade 3 and 4); all other treatment-related adverse events were Grade 1 or 2 with the most common (> 10%) being fatigue (30%), nausea (17%), and chills (12%). Serum Tregs and eosinophils (both express trimeric IL-2Rs) decreased in patients across all cohorts while NK and CD8 cell serum concentrations trended upwards. The CD8 to Treg ratio continues to trend upward in patients across each study arm. Of the response evaluable patients, a best response of stable disease occurred in 4 patients on Arm 1A (including a 15% target lesion decrease in a patient with non-small cell lung cancer who progressed on chemo+anti-PD-L1), and 1 melanoma patient on Arm 1B who progressed on anti-CTLA-4 + anti-PD-1 therapy, with a 25% tumor target lesion decrease. AU-007 PK demonstrates dose proportional increases in serum concentrations and no evidence of ADA.

Conclusions AU-007 +/- aldesleukin reduces serum Tregs and increases NK and CD8 cell serum concentrations trended upwards. The CD8 to Treg ratio continues to trend upward in patients across each study arm. Of the response evaluable patients, a best response of stable disease occurred in 4 patients on Arm 1A (including a 15% target lesion decrease in a patient with non-small cell lung cancer who progressed on chemo+anti-PD-L1), and 1 melanoma patient on Arm 1B who progressed on anti-CTLA-4 + anti-PD-1 therapy, with a 25% tumor target lesion decrease. AU-007 PK demonstrates dose proportional increases in serum concentrations and no evidence of ADA.

Trial Registration NCT05267626