670 DEVELOPMENT OF A ROBUST MANUFACTURING PROCESS FOR AB-1015, AN INTEGRATED CIRCUIT T CELL (ICT) PRODUCTS, USING TARGETED, CRISPR INTEGRATION OF TRANSGENES BY ELECTROPORATION (CITE) EDITING

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Background AB-1015 is an autologous, integrated circuit T cell (ICT) product for the potential treatment of platinum-resistant ovarian cancer. AB-1015 includes a transgene cassette with an 'AND' logic gate designed to limit off-tumor toxicity through dual tumor antigen recognition and a dual shRNA-miR designed to resist TME suppression and to improve ICT cell function. ICT cells are generated via CRISPR integration of transgenes by electroporation (CITE), a non-viral and site-specific integration approach with the goal to provide enhanced safety and increased cargo capacity. Scalable, semi-closed, and semi-automated manufacturing processes were developed to support GMP manufacture for Ph1 clinical evaluations. Subsequently, the process was optimized to improve transgene integration frequency and prepared for GMP implementation. Phase 1 clinical investigation is currently ongoing.

Methods On Day 0, CD4 and CD8 positive cells were isolated from fresh apheresis. Cells were activated using CD3/CD28 stimulation, electroporated with Cas9 protein, sgRNA targeting a safe harbor site (GS94), and plasmid DNA encoding the transgene. Cells were expanded until harvest and formulated into drug product. Frozen cell drug product was thawed and characterized using flow cytometry and in vitro functional assays for release and characterization.

Results Processing of apheresis using the AB-1015 manufacturing process resulted in average knock-in efficiencies and total therapeutic yields exceeding dose level needs. In addition to robust IFN-γ production and tumor cell killing in dual antigen-specific co-culture, ICT cells retained favorable memory phenotype (CCR7+) at harvest. Similar knock-in efficiencies and comparable phenotype and function were observed for clinical AB-1015 products in comparison to preclinical healthy donors.

Conclusions A robust, 10-day manufacturing process was successfully developed for AB-1015 that enables knock-in of a large (> 6 kb) transgene using a site-specific, non-viral integration approach. Billions of ICT cells can be generated from a single healthy donor in a semi-closed, semi-automated fashion and these ICT cells display potent anti-tumor activity in vitro and in vivo with high specificity in preclinical studies. AB-1015 is currently in Phase 1 clinical trials.

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