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MANUFACTURE OF ALLOGENEIC, HLA-MATCHED, TCR-EDITED T-CELL THERAPY REACTIVE AGAINST MINOR HISTOCOMPATIBILITY ANTIGEN 1 TO TREAT ACUTE MYELOID LEUKEMIA IN COMBINATION WITH CD34 HSCT WITH THE POTENTIAL FOR HIGH POTENCY AND DURABILITY

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Background BlueSphere Bio (BSB) has developed a proprietary high-throughput T cell receptor (TCR) capture and screening platform to enable T-cell therapy for the treatment of cancer. Our TCX-101 program develops allogeneic TCR T-cells to enhance the beneficial alloreactive T cell response observed with allogeneic hematopoietic stem cell transplantation (alloSCT). The therapeutic goal is to promote a graft-versus-leukemia effect, whilst reducing the risk of graft versus host disease. The first product in the platform, BSB-1001, targets the hematopoietically-restricted minor HA-1 (HA-1 TCR). HA-1 is restricted by a common human HLA type A*02:01 and covers approximately 50% of the that population. BSB-1001 is currently in development for clinical testing in Acute Myeloid Leukemia (AML).

Methods BSB-1001 is generated by activation of healthy donor PBMCs from a mobilized apheresis, using anti-CD3 OKT3. Following the activation, CD8 T-cells are isolated, and the endogenous TCR knocked out with CRISPR edits, using formulated Cas9/guide RNA, RiboNuclear Particles (RNP). Cells are then transduced with the anti-miHA-1 TCR lentivector (Yposkesi). Cells are cultured and expanded and cryopreserved on harvest day using CryoStor10 in a controlled rate freezer. The product is co-administered with CD34 cells isolated from the same donor apheresis.

Results BSB-1001 was developed and generated at BSB. PBMCs derived from fresh APH are activated using OKT3, with T-cells over 90% by CD69 upregulation. CD8+ T-cells were isolated, and endogenous TCR knockout using RNP, and then transduced with anti-HA1 TCR lenti viral vector. Integrated vector copy number in these cells is under 5 copies/cell. After culture, day 12 harvest, and cryopreservation, cells are thawed and tested in QC. Phenotype of these cells demonstrates a generally stem-cell like phenotype (Tcm, Tem, Tscm), with Tscm cells predominating. BSB-1001 cells showed efficient killing of HA-1+ LCL222 cells, but not HA-1 -/- LCL224 cells. Log-scale plots shows strong IC50 points on the killing curve as low as 0.1:1 Effector:Target ratios. Continued culture of the cells after killing is measured, by the addition more LCL cells, shows that the cytolytic potency of the cells is maintained for at least an additional 20 days (32 days from initial activation).

Conclusions Taken together, the results indicate that BSB-1001 is an active, highly potent drug product candidate, with a potential to be effective in treating HA-1+ HLA-A*02:01 AML patients in the setting of alloSCT. The phenotype and high cytolytic bioactivity indicate that the clinical response has a potential to be very potent and durable.

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