**Background**: B-cell targeted therapeutics have shown efficacy in the treatment of autoimmune disorders, providing the impetus to develop strategies that target the B-cell receptor. In this study, MacroGenics, Inc., designed and developed MGD010, a bispecific DART molecule, with the potential to modulate B-cell activation. MGD010 binds CD32B, (FcγRIIb) via its simultaneous colligation with the BCR component, CD79B. Initial Phase 1 trials performed in healthy subjects demonstrated MGD010 was well tolerated at 10 mg/kg and showed linear PK and dose-dependent B-cell receptor occupancy with a reduced propensity for B-cell activation in the absence of B-cell depletion. An expansion cohort study was undertaken to effect the question of MGD010 on the immune response to an antigen (hepatitis A vaccine, HAV) in healthy subjects.

**Materials and Methods**: In a placebo-controlled, randomised, open-label study of 42 healthy male or female subjects (aged 18–46 years) at 6 US sites, 20 received placebo and 20 received MGD010 (3 mg/kg or 10 mg/kg). Serum was collected prior to dosing and at each time point after dosing to measure MGD010 levels by quantitative CMIA. The maximum concentration (Cmax) and time to reach Cmax (Tmax) were measured. To achieve maximum inhibition of B-cell activation in vitro, MGD010 was introduced into a 5-day culture (3 pg/mL) of CD19+ naïve B cells. Naïve B cells were cultured in the presence or absence of MGD010 and re-stimulated with an anti-human IgM F(ab’)2 antibody for 5 days in the presence or absence of MGD010. The HAV-IgG titers were determined by quantitative CMIA. Samples with signal/cut-off values ≥1.00 were considered to be positive (seroconversion).

**Conclusions**: Twenty-four (24) healthy subjects were enrolled for the study and 23 completed. Of the 20 subjects completing the study, 12 received placebo and 8 received MGD010. The only serious adverse event reported was in a subject who had a reaction to the placebo vaccine. The HAV seroconversion rates for placebo and MGD010 were 30% and 68%, respectively. The seroconversion rate trended in the expected direction in the dose-escalation group. These data support further development of this therapeutic modality for autoimmune disorders.

**Abstract**

**Objectives**: To assess safety and efficacy of MGD010 on HAV response across 2 dose levels: 3 mg/kg and 10 mg/kg and show linear PK and dose-dependent B-cell receptor occupancy with a reduced propensity for B-cell activation in the absence of B-cell depletion.

**Results**: Twenty-four (24) healthy subjects were enrolled for the study, and 23 completed. Of the 20 subjects completing the study, 12 received placebo and 8 received MGD010. The only serious adverse event reported was in a subject who had a reaction to the placebo vaccine. The HAV seroconversion rates for placebo and MGD010 were 30% and 68%, respectively. The seroconversion rate trended in the expected direction in the dose-escalation group. These data support further development of this therapeutic modality for autoimmune disorders.

**Conclusion**: MGD010 was confirmed to be safe and well tolerated in healthy subjects as a single administration of 3 or 10 mg/kg, with dose-proportional PK and all dose levels resulted in full receptor occupancy, with dose-proportional saturation decay. MGD010 inhibited downmodulation of BCR expression levels (as previously reported), together with a decrease in B-cell CD40 expression. MGD010 inhibited CD40-promoted B-cell activation and IgG secretion. Consistent with its mechanism of action, a single administration of MGD010 inhibited the humoral response to hepatitis A vaccine at both dose levels. These data support further development of this therapeutic modality for autoimmune disorders.

**Reference**


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**MacroGenics, Inc., Rockville, Maryland, USA**

**SAT0027**

**Immunomodulatory Effects of MGD010, a DART® Molecule Targeting Human B-cell CD32B and CD79B**

Wei Chen, Sadhna Shankar, Joanna Lohr, Xiao-Tao Yao, Haiquan Li, Xiaoru Chen, John Muth, Neely Gal-Edd, Ezio Bonvini, Syd Johnson, Naimish Pandya, Paul A. Moore, and Jon Wigginton