M281: A Therapeutic FcRn Blocking Antibody for Rapid Clearance of IgG and IgG Autoantibodies in Immune Cytopenias and other Autoimmune Diseases

Leona E. Ling, Sucharita Roy, Thomas Daly, Edward Cochran, Steven Tyler, Lynn Markowitz, Dorota A. Bulik, Jay Duffner, Amit Choudhury, James Meador, Sandra Sipse, Srishti Gurani, Stan Lee, Nathaniel Washburn, Robin Mecciorri, John Scheck, Jing Wang, Alison Long, Laura Rutitzky, Birgit Schulte, Jan Hillson, William Averey, Ganesh V. Kaundinya and Anthony M. Manning — Momenta Pharmaceuticals, 675 West Kendall Street, Cambridge, MA 02142

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INTRODUCTION
IFN-γ is the primary pathogenic cytokine in a number of autoimmune diseases. Efficacious treatment which decreases systemic levels of pathogenic antibodies include treatment with IVIG, therapeutic plasmapheresis or immunoadsorption. Here, a novel strategy was evaluated to induce IgG clearance in disease driven by IgG autoantibodies by blockade of FcRn-mediated IgG recycling.

M281: A High Affinity Human FcRn-blocking Monoclonal Antibody
M281 was developed as a high affinity, non-fusion, human IgG1 antibody to block FcRn binding to IgG. M281 effect on IgG recycling was demonstrated in patients and normal healthy volunteers. Systemic levels of pathogenic antibodies include treatment with IVIG, therapeutic plasmapheresis or immunoabsorption.

METHODS
M281 was developed as a high affinity, non-fusion, human IgG1 monoclonal antibody. M281 effect on IgG recycling was evaluated in humanized rodent models in vivo. In vitro studies in transgenic human FcRn knock out mice and cynomolgus monkey were performed to characterize the pharmacokinetic, pharmacodynamics and target occupancy in peripheral blood mononuclear cells. M281 also induced clinical benefit in mouse models of rheumatoid arthritis.

RESULTS
M281 demonstrates specific dose-dependent, albumin sparing IgG clearance in human FcRn transgenic/mouse FcRn null mice and in cynomolgus monkeys. M281 inhibits IgG recycling in endothelial cells in vitro. Pharmacokinetic, target occupancy, pharmacodynamics and biodistribution indicate target-related antibody distribution with rapid, dose-dependent target occupancy and systemic clearance. M281 was also demonstrated efficacy in mouse models of autoimmune disease.

CONCLUSIONS
These findings support the evaluation of M281 as a strategy for the rapid and irreversible suppression of pathogenic autoantibodies in patients with immune cytopenias, acquired inhibitors, thrombotic thrombocytopenic purpura and collagen antibody-induced arthritis of immune origin.

REFERENCE

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