ARQ-234: a high affinity CD200-Fc fusion protein for the treatment of atopic dermatitis
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Background: Human CD200 receptor (CD200R, CD200R1), originally OX2R, is an inhibitory immune checkpoint receptor expressed on many myeloid cells, and lymphocyte populations including CD4 T and ILC2 cells, signaling via DOK2 and Erk/MAP kinases to inhibit the NFκB pathway and cytokine secretion. Its ligand, CD200, is expressed on the surface of tissues including endothelium, epithelia and neurons, where it moderates immune activation particularly at barrier sites including lung, skin and the GI tract. Published evidence, including GWAS studies, implicates dysregulation of the CD200 axis in many allergic, autoimmune and inflammatory diseases. Furthermore, a CD200R agonist antibody has demonstrated efficacy in an early phase clinical trial of moderate to severe atopic dermatitis patients.

Methods: We have engineered high affinity soluble CD200R agonists, comprising human CD200-Fc proteins with substantially increased (up to 130-fold) monomeric binding affinity for CD200R.

Results: High affinity human CD200-Fc a) out-performs wild type in inhibiting IL-6 release from a cell line expressing high levels of human CD200R, b) has superior potency to a CD200R agonist antibody in a humanized mouse model of contact hypersensitivity, and c) substantially reduces cell infiltrate in bronchoalveolar lavage fluid in a non-human primate model of airway
inflammation. A high affinity murine CD200-Fc has been engineered for additional proof-of-concept studies, and is more potent than wild type in an *in vivo* model (collagen-induced arthritis). Finally, we describe ARQ-234, a high affinity CD200-Fc protein with antibody-like serum half-life in NHP, due to the introduction of mutations in the Fc domain which increase relative binding to the neonatal Fc receptor at low (endosomal) pH. ARQ-234 is currently in pre-clinical development as a therapeutic for atopic dermatitis.

**Keywords**: ARQ-234, atopic dermatitis, CD200-Fc protein, inhibitory immune checkpoint receptor, preclinical