Discovery of ARN-6039 as a Potent, Orally Available Inverse Agonist of RORγt for Autoimmune Neuroinflammatory Demyelinating Disease

*John W. Rose,[2,3] Noel G. Carlson,[3] Venkatakrishnareddy Yerramreddy,[1] Rajendra P. Appalaneni,[1] Jeff A. Handler,[1] Ramamohan R. Kancherla[1] and *±Hariprasad Vankayalapati,[1]

[1]Early Discovery and Medicinal Chemistry, Arrien Pharmaceuticals, 9980 South, 300 West, Suite # 200, Salt Lake City, UT 84070, USA, [2]Division of Neuroimmunology, Imaging and Neurosciences Center, 729, Arapeen Way, University of Utah, Salt Lake City, UT 84108, USA, [3]Neurovirology Research Laboratory, VA SLC HCS, 500 Foothill Dr., Salt Lake City, UT 84148, USA.

*Corresponding/±Presenting authors

OBJECTIVE: To evaluate the effect of the ARN-6039 on inhibiting RORγt-activated IL-17A, in vivo therapeutic MOG_{35-55} induced EAE and safety/tolerability IND experimental model studies.

BACKGROUND: RORγt is a key transcription factor and master regulator of human Th_{17} cells, a unique subset of $CD4^+$T cells. RORγt controls cellular differentiation, function and IL-17 producing T-helper lymphocyte release by Th_{17} cells and help in mediating the immunopathology of human autoimmune Multiple Sclerosis (MS).

DESIGN/METHODS: ARN-6039 was tested in vitro for the activation of CD4+T lymphocytes to Th17 cell differentiation and IL-17 production. In vivo efficacy of ARN-6039 on inhibition, cytokine-IL-17 production and EAE efficacy studies were conducted using BALB/c and C57BL/6 mouse models.

RESULTS: The activity of ARN-6039 against RORγt was demonstrated in a RORγt-activated IL-17A Prom/LUCPorter assay in HEK 293 cells (360 nM) and in IL-17 release from $CD4^+$T cell assays (220 nM). The compound also possesses ideal CNS drug-like criteria, exhibited excellent pharmacokinetics (%F: 37), pharmacodynamics, and correlative PK/PD and ADME characteristics. The up-take data indicates that ARN-6039 may act in the CNS as well as the blood to inhibit inflammation and demyelination. Oral administration of ARN-6039 also exhibits promising efficacy in EAE, and extended to 0 on day 18 to until day 28. Additionally, the AUC and the mean cumulative scores at doses 10, 20, 30, 40 mg/Kg showed a significant reduction when compared to untreated group when ARN-6039 was administered after onset of disease. Moreover, ARN-6039 showed no signs of toxicities up to doses 2000 mg/Kg from our GLP-Toxicity studies. In vitro, biomarker profiling for human immune cells will be presented.

CONCLUSIONS: The results from these studies demonstrate that ARN-6039 may be an effective therapeutic agent in MS models and a potential disease-modifying therapy for MS. Assessments and preparations for clinical trials in MS are underway.

Study Supported By: Arrien Pharmaceuticals

Disclosure: J.W.R, None**, N.G.C,** None**, V.Y,** Arrien Pharmaceuticals, **R.P.A,** Arrien Pharmaceuticals**, J.A.H,** None, **R.R.K**, Arrien Pharmaceuticals and **H.V**, Arrien Pharmaceuticals