ATI-450: A Novel MK2 Pathway Inhibitor - Preclinical & Clinical Translational Studies to Predict Human Dose

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ATI-450 is a mechanistically novel, investigational inhibitor of the mitogen-activated protein kinase (MAPK)–activated protein kinase 2 (MK2) pathway, downstream of p38 MAPK. It selectively targets the p38MAPK/MK2 complex and locks MK2 in an inactive conformation thereby preferentially inhibiting MK2 activation relative to alternate p38 MAPK substrates. Due to p38 MAPK proinflammatory actions being largely mediated by MK2, selective blockade of this pathway bypasses p38 MAPK–regulated anti-inflammatory and negative feedback substrates. ATI-450 inhibited the p38MAPK/MK2 complex with an IC50 = 16.7 ± 5.6nM while demonstrating selectivity for the p38MAPK/PRAK and p38MAPK/ATF2 complexes of ≥ 700x.

ATI-450 demonstrated concentration-dependent inhibition of cytokine production and phosphorylation of the MK2 substrate HSP27 in the U937 cell line, rheumatoid arthritis synovial fibroblasts and human whole blood (HWB) following stimulation with inflammatory stimuli including LPS (TLR4), IL-1b, PolyI:C (TLR3) and R848 (TLR7/8). HWB was utilized as the most physiologically relevant cellular system to evaluate potency of ATI-450 in blocking cytokine production. ATI-450 potency for blocking TNFa and IL1b in HWB in response to LPS ranged in IC50 values from 12nM – 29nM. The biochemical efficiency for ATI-450 is high (>1) based on free-fraction corrected HWB potency relative to biochemical potency for blocking the p38MAPK/MK2 complex.

ATI-450 showed attenuation of LPS-induced cytokine production in both in vivo rat and mouse studies with EC50’s in the 0.5–2.0 mg/kg range. In the rat streptococcal cell wall arthritis model, both edema and bone loss were reduced by ATI-450 at doses and drug levels in line with whole blood in vitro studies and in vivo acute LPS induced cytokine inhibition. An admix chow formulation of ATI-450 (1000ppm) demonstrated activity in the mouse collagen induced arthritis model with steady state drug plasma levels approximating IC50 concentrations in the mouse LPS study. A direct translation of ATI-450 potency from cellular HWB studies to in vivo rodent endotoxemia and arthritis models was observed and utilized for a human phase 1 dose projection plan.

ATI-450 was evaluated in phase 1 SAD/MAD studies at doses from 10mg to 120 mg. Ex vivo LPS stimulated cytokine pharmacodynamic (PD) analysis demonstrated dose- and exposure-dependency. The target PD modulation associated with phase 2 dose selection was 80+% inhibition of LPS induced TNFa at trough. The 50mg BID dose inhibited ex vivo stimulated TNFa production between ~85% at trough and ~93% at peak concentrations following seven days of dosing in the MAD study. The exposure/response relationship associated with the 50mg BID dose was predicted from the HWB potency of ATI-450. A 12-week rheumatoid arthritis (RA) phase 2a study was conducted using the 50mg BID dose. Ex vivo LPS-stimulated cytokine inhibition in blood from RA patients and volunteers dosed with ATI-450 at 50mg BID was comparable. Further, RA clinical improvement across multiple endpoints was also observed in this study. This sequence of studies demonstrates the power in utilizing translatable cellular and animal models to predict human phase 1 and 2 dosing.