534 Long-term Quality of Life and Safety in Patients with Indolent Systemic Mastocytosis Treated with Avapritinib in the PIONEER Study

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RATIONALE: Indolent systemic mastocytosis (ISM) is a clonal mast cell disease primarily driven by the *KIT* D816V mutation characterized by debilitating cutaneous, gastrointestinal, neurological, and musculoskeletal symptoms. Progressive symptoms can lead to life-threatening anaphylaxis, poor quality-of-life (QoL), and significant morbidity. Avapritinib, a selective KIT D816V inhibitor, is approved in adult patients with ISM in the EU and the US.

METHODS: Patients with moderate-to-severe ISM with symptoms inadequately controlled despite best supportive care (BSC), were enrolled in the randomized, double-blinded, placebo-controlled PIONEER study and assigned to avapritinib or placebo, both with BSC, followed by an open-label extension. QoL and symptom burden were assessed using 12-Item Short-Form Health Survey (SF-12®), Mastocytosis Quality-of-Life Questionnaire (MC-QoL), European Quality-of-Life 5 Dimensions (EQ-5D®), Patient Global Impression of Severity (PGIS), and Patient Global Impression of Change (PGIC). Long-term safety was also assessed.

RESULTS: A total of 226 patients initiated 25 mg once-daily (QD) avapritinib including 75 patients who received placebo and crossed over to open-label 25 mg QD avapritinib. Longer-term data with >2 years of follow-up demonstrated durable improvement in symptoms and QoL (SF-12, MC-QoL, EQ-5D, and PGIS measures, and benefit on the PGIC). Compared to initial findings from PIONEER, no new safety concerns were identified with longer exposure. Treatment-related adverse events were similar to the previous report.

CONCLUSIONS: Avapritinib-treated patients continued to experience improvements in symptoms and QoL measures through >2 years of follow-up. Avapritinib plus BSC was generally well-tolerated with longer-term treatment.

535 BLU-808: A Potent and Selective Oral Small Molecule Wild-Type KIT Tyrosine Kinase Inhibitor for Allergic Conditions

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RATIONALE: Mast cells are involved in multiple allergic diseases including but not limited to chronic urticaria, Type 2 asthma, rhinitis, atopic dermatitis, food allergy, and prurigo nodularis. BLU-808 is a potent, selective, orally available, investigational inhibitor of wild-type (WT) KIT capable of reducing mast cell activation and eliminating mast cells in preclinical models. Mice deficient in mast cells due to inactivating mutations in KIT are less susceptible to airway hyperresponsiveness, however the impact of WT KIT inhibition in the setting of intact mast cells has yet to be fully explored. By studying the effect of KIT inhibition and the degrees to which mast cells are inhibited and/or depleted, the utility of KIT inhibitors in allergic diseases can be further defined.

METHODS: Airway hyperresponsiveness in a preclinical rodent model of allergic asthma was measured alongside mast cell numbers after BLU-808 treatment. Several dosing regimens were explored including dose level and duration. Clinically relevant combination therapies were also tested.

RESULTS: BLU-808 blocked airway hyperresponsiveness both with short- and long-term treatment, at times with minimal or no impact on mast cell number. The effect of BLU-808 on mast cell activation and mast cell viability *in vitro* mirrored that seen *in vivo*.

CONCLUSIONS: BLU-808 is efficacious in a preclinical rodent model of asthma. Mast cell inhibition may be a promising therapeutic for other allergic diseases.

536 A novel mouse model for the study of Alpha-Gal Syndrome

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RATIONALE: Alpha-gal syndrome (AGS) is an allergic condition characterized by an IgE-mediated reaction to galactose-alpha-1,3-galactose (alpha-gal). Alpha-gal is a unique carbohydrate epitope absent in humans but naturally produced on glycolipids and glycoproteins in non-primate mammals, prosimians and New World monkeys. In the US, lone star tick bites are known to induce production of alpha-gal specific IgE, resulting in IgE-mediated allergic reactions to mammalian meat and alpha-gal containing products. To date, published mouse models of AGS are largely reliant on mouse production of alpha-gal IgE. Herein, we describe a mouse model of AGS that utilizes passive sensitization with human plasma to allow for interrogation of the polyclonal human alpha-gal IgE-mediated allergic response.

METHODS: Fc-epsilon receptor 1 alpha (FceR1a) humanized, alpha-1,3-galactosyl transferase knockout ($Fcer1a^{hu/hu}/GGTA\ 1^{-/-}$) mice were generated using Regeneron's VelociGene technology. Specifically, the gene encoding endogenous mouse FceR1a was replaced with the corresponding human sequence and the gene encoding alpha-1,3-galactosyl transferase, the enzyme that makes the alpha-gal epitope was deleted. Absence of alpha-gal epitopes in splenocytes harvested from $Fcer1a^{hu/hu}/GGTA1^{-/-}$ mice was confirmed by flow cytometry and the passive cutaneous anaphylaxis mouse model of mast cell degranulation was utilized to confirm an alpha-gal-induced allergic response.

RESULTS: Alpha-gal epitopes were detected in splenocytes harvested from $Fcer1a^{hu/hu}/GGTA1^{+/+}$ but not $Fcer1a^{hu/hu}/GGTA1^{-/-}$. Following sensitization with human AGS plasma, mast cell degranulation was achieved upon challenge with alpha-gal containing reagents including galactose-alpha-1,3-galactose and galactose-alpha-1,3-galactose-N-acetyl glucosamine conjugated to human serum albumin or bovine serum albumin.

CONCLUSIONS: $Fcer1a^{hu/hu}/GGTA1^{-/-}$ mice present as a novel model to study of AGS and therapeutic interventions thereof.