SATURDAY

441 Briquilimab, An Anti-CD117 Antibody, Prevents Cockroach Allergen Induced Allergic Asthma In Mice Expressing Chimeric Human And Mouse CD117

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RATIONALE: Stem cell factor (SCF) signaling through c-Kit (CD117) plays a key role in mast cell (MC) differentiation and survival. Inhibition of this pathway has the potential to treat MC-mediated diseases including allergic asthma. Briquilimab is a humanized aglycosylated monoclonal antibody against CD117 that inhibits SCF signaling and can deplete human MCs.

METHODS: Transgenic mice expressing chimeric CD117 (hmCD117), consisting of human extracellular and mouse intracellular regions of CD117 in lieu of wild-type mouse CD117, were generated. Allergic asthma was induced in hmCD117 mice by intranasal exposure to cockroach allergen (CRA). Briquilimab's effects on airway hyperresponsiveness (AHR), airway inflammation, and lung MC count were evaluated by lung function test, bronchoalveolar lavage (BAL), and lung histology.

RESULTS: The intranasal sensitization and challenges of hmCD117 mice by CRA (10 mcg/mouse, days 1, 2, 15, 18, and 21) led to airway eosinophilia and AHR to the similar extent observed in CRA-exposed wild-type mice. A single dose of briquilimab (*i.p.* 60 mg/kg, day 3) markedly reduced the numbers of lung MCs (briquilimab-treated 14 ± 2 *vs.* untreated 51 ± 9 [cells/mm^2], $P<0.05$) and BAL-recovered eosinophils (briquilimab-treated 8.96 ± 5.85 *vs.* untreated 57.81 ± 10.07 [x10^4 cells], $P<0.05$) measured at necropsy (day 22), which was comparable to BAL eosinophils in CRA-exposed MC-deficient KitW-sh/W-sh mice (4.44 ± 1.05 [x10^4 cells], $P=0.355$). Moreover, airway-infiltrated eosinophils and neutrophils, as well as AHR, were also significantly decreased in briquilimab-treated mice, suggesting briquilimab prevents allergic asthma via MC depletion.

CONCLUSIONS: This study provides evidence that briquilimab has the potential to be a novel therapeutic agent for allergic asthma and eosinophilic disorders.

442 Impact of Patient Baseline Characteristics On Work Productivity and Activity Impairment Following Omalizumab Treatment In Patients With Allergic Asthma

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RATIONALE: The anti-IgE antibody omalizumab is effective for patients with moderate-to-severe allergic asthma, but the impact of baseline patient characteristics on work productivity and activity impairment is unclear.

METHODS: The prospective, observational EXCELS study (NCT00252135) followed patients ≥12years with moderate-to-severe persistent asthma treated with/without omalizumab for ≤5years. This longitudinal post-hoc analysis included patients who received (n=5006) and did not receive omalizumab (n=2830). The omalizumab group was further categorized by omalizumab start time: >7 days before baseline visit (established users; n=4419) or 7 days before to 30 days after baseline visit (new starters; n=587). Asthma-related work, school, and activity impairment was measured over 24months post-index using the Work Productivity and Activity Impairment–Asthma (WPAI-Asthma) questionnaire (range: 0-100); higher scores indicate more impairment. The impact of baseline characteristics on WPAI-Asthma scores was summarized descriptively.

RESULTS: Omalizumab new starters experienced rapid reductions in mean WPAI-Asthma scores (baseline vs month 6: work 26 vs 13; school 15 vs 9, regular activities 35 vs 21); both omalizumab cohorts had reductions from baseline maintained to 24months. For new starters and established omalizumab users, changes in WPAI-Asthma scores did not appear influenced by any baseline characteristics explored (BMI [<30 vs ≥30kg/m^2], asthma severity [moderate vs severe], time since diagnosis [<20 vs ≥20years], age [<45 vs ≥45years], smoking history [current/former vs never], oral corticosteroid use [long-term/periodic vs none], sex [male vs female], total IgE [above/below median 166IU/mL]).

CONCLUSIONS: Rapid and sustained improvement in work productivity and activity was reported following initiation of omalizumab, and did not appear impacted by baseline characteristics explored.

443 Safety and Pharmacokinetics of Single Ascending Doses of KN-002 in Healthy Volunteers and Multiple Ascending Doses of KN-002 in Subjects With Mild Asthma

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RATIONALE: KN-002 is a potent pan-JAK inhibitor, formulated as a dry powder for oral inhalation, designed to interrupt the inflammatory cascades implicated in the pathogenesis of eosinophilic and non-eosinophilic moderate to severe asthma.

METHODS: This Phase 1, randomized, double-blinded, placebo-controlled 4-part study (NCT05006521) was conducted at Medicine Evaluations Unit, Manchester, UK and evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of KN-002. In Part 1, single ascending doses (0.2 to 12 mg or matched placebo) were administered to 6 cohorts (6Active/2Pbo) of healthy volunteers. In Part 2, ascending repeat doses (0.6 mg QD to 8 mg BID or matched placebo) were administered over 10-days to 4 cohorts (6Active/2Pbo) of subjects with mild asthma.

RESULTS: 49 Part 1 (37 on KN-002) and 32 Part 2 (24 on KN-002) subjects received treatment. PK was dose proportional with systemic plasma concentrations below previously determined pharmacologically active levels. Steady state PK was achieved by approximately Day 3 with minimal accumulation following repeat dosing. No serious, severe, or treatment-related adverse events were reported. A single subject withdrew (COVID-19 related). Overall, the most common AE was headache. No relevant findings among safety measures were observed.

CONCLUSIONS: Using an inhaled route of delivery, KN-002 was well tolerated with low systemic exposure and no safety concerns identified following single (≤12 mg) and 10-day repeat dosing (≤8 mg BID) in healthy volunteers and subjects with mild asthma, respectively. Outcomes support the Phase 2 clinical development of KN-002 in subjects with moderate to severe asthma not controlled on ICS/LABA treatment.