789 Integrated Safety And Efficacy Of Garadacimab For Hereditary Angioedema Prophylaxis Across 3 Clinical Trials: Phase 2, Pivotal Phase 3, And Open-Label Extension Studies

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RATIONALE: Hereditary angioedema (HAE) attacks are unpredictable and debilitating. We report integrated safety and efficacy across Phase 2, pivotal Phase 3, and open-label extension (OLE) studies evaluating garadacimab (anti-activated factor XII monoclonal antibody) for HAE prophylaxis.

METHODS: Subcutaneous garadacimab was evaluated in an integrated analysis comprising Phase 2 (12-week placebo-controlled period with subsequent open-label period; 75/200/600 mg once-monthly or 400 mg once every 2 weeks), pivotal Phase 3 (6-month placebo-controlled period), and >12-month OLE studies (both 200 mg once-monthly). Endpoints included treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs, per protocol: thromboembolic/abnormal bleeding events, severe hypersensitivity/anaphylaxis) and efficacy.

RESULTS: Overall, 172 patients received garadacimab (any dose; median [range] exposure 1.3 [0.2–4.2] years; 83.1% and 19.2% had ≥1 and ≥2 years' exposure, respectively). Of these, 148/172 (86%) experienced ≥1 TEAE (97.6% mild/moderate), an exposure-adjusted rate of 3.1 TEAE/patient-year. Seven patients experienced SAEs, none garadacimab-related. One AESI per protocol was experienced by 1 patient (Phase 2, 600 mg, epistaxis, not garadacimab-related). The most common garadacimab-related TEAEs were mild/moderate injection-site reactions. Per integrated efficacy set, the mean (standard deviation) monthly attack rate in garadacimab 200 mg-treated patients (n=164) was 0.17 (0.40) versus 3.55 (2.40) during run-in, corresponding to a 94.2% reduction. Over a median 1.2 years' observation, the majority of garadacimab-treated patients (94/164, 57.3%) remained attack-free. No placebo-receiving patients (n=25) were attack-free.

CONCLUSIONS: These data further corroborate the robust garadacimab efficacy over >1 year for long-term HAE prophylaxis along with the favorable and consistent safety profile so far observed.

790 Withdrawn

791 Endogenous Chemerin Limits the Severity of Ozone-Induced Airway Hyperresponsiveness Irrespective of Body Mass

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RATIONALE: Tumor necrosis factor-α, a pleiotropic adipocytokine, limits the severity of airway hyperresponsiveness (AHR), a cardinal feature of asthma, in obese mice exposed to ozone (O_3), a criteria pollutant and non-atopic asthma stimulus. However, in this phenomenon, the contribution of chemerin, an adipocytokine and non-chemokine chemoattractant for natural killer cells, macrophages and plasmacytoid dendritic cells, is unknown. Consequently, our goal was to asseverate the relevance of chemerin in the development of O_3-induced AHR in obesity.

METHODS: Wild-type C57BL/6J mice and mice genetically deficient in chemerin (chemerin-deficient mice) were fed standard chow or a diet consisting of 60 kcal % fat (high-fat diet; HFD) from weaning until 30 weeks of age. At 30 weeks of age, mice were exposed to either filtered room air (air) or O_3 (2 ppm) for three hours. Twenty-four hours following cessation of exposure, indices of airway responsiveness to methacholine [airway resistance and coefficients of lung tissue damping and elastance] were measured using the forced oscillation technique.

RESULTS: Consumption of a HFD by wild-type and chemerin-deficient mice led to obesity. Following air exposure, airway responsiveness to methacholine was greater in chemerin-deficient as compared to wild-type mice irrespective of the diet consumed. All mice exposed to O_3 exhibited AHR. Nevertheless, regardless of the diet consumed, airway responsiveness was greater in chemerin-deficient as compared to wild-type mice following O_3 exposure.

CONCLUSIONS: Chemerin limits the severity of airway responsiveness in the presence and absence of inciting stimuli and may be a therapeutic target to limit exaggerated airway narrowing observed in obese and non-obese asthmatics.

792 Biomarkers of Oxidative Stress Associated with Radon Exposure in the School Inner-City Asthma Study (SICAS)

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RATIONALE: Radon is an omnipresent radioactive gas recently reported to be associated with increased asthma morbidity. We aimed to identify biomarkers associated with radon exposure and hypothesized elevated radon-derived particle radioactivity exposure would be associated with increased inflammatory biomarker levels.

METHODS: In a panel of 299 school children with asthma enrolled in the School Inner-City Asthma Study, we assessed estimated radon exposure (1- and 2-month averaged radon) by geospatial model with lung function and inflammatory biomarker outcomes.

RESULTS: In a total of 139 observations, we found a significant increase in IL-8 and bFGF, cytokines described to be associated with oxidative stress and asthma, and modeled radon exposure. Higher radon was significantly associated with greater increase in bFGF compared to low radon exposure (n=299, obs=139; 1-month moving radon average [effect estimate % change = 2.72, 95% CI 0.11-5.41]; 2-month moving radon average [effect estimate % change = 2.59, 95% CI 0.11-5.41]). Higher radon was significantly associated with greater increase in IL-8 compared to low radon exposure (n=299, obs=139; 1-month moving radon average [effect estimate % change = 6.86, 95% CI 1.54-12.46]; 2-month moving radon average [effect estimate % change = 6.86, 95% CI 1.59-12.40]).

CONCLUSIONS: Radon is a novel modifiable risk factor for asthma recently reported to be associated with asthma morbidity. This work identifies important biologic disease pathways via biomarkers that may be central to the exposure-outcome relationship.