Eastern Allergy Conference
June 2-5, 2022 ~ Palm Beach, FL

Scientific Posters F1-F32 will be on display in the Ponce Foyer during the coffee break, 10:15-11:00am, Friday June 3, 2022

Not for
CME Credit

F1

Rationale and Design for Randomized, Double-Blind, EDS-Placebo–Controlled Trials of EDS-FLU in Chronic Rhinosinusitis

James N Palmer, MD[1], and the ReOpen Steering Committee.

Background: While several treatments are FDA-approved for nasal polyposis, there are no FDA-approved treatments for CRS broadly, specifically for CRS without nasal polyps. FDA guidance stated that a medication for CRS should demonstrate benefits for both symptomatic and objective signs of sinus disease. We aim to evaluate and address the challenges in designing clinical studies for medications intended to treat CRS. The rationale and design reported here will provide guidance for future clinical trials.

Methods: In the absence of a standardized drug development pathway for CRS, a panel of experts developed a novel study design for the exhalation delivery system with fluticasone (EDS-FLU) that meets the criteria set forth in prior FDA draft guidance and is feasible to conduct and generalizable to the CRS population.

Results: Two similar 24-week, double-blind, placebo-controlled trials were developed with co-primary endpoints of change in (1) symptom severity score (composite of nasal congestion, facial pain/pressure, and nasal discharge); and (2) volumetric assessments of sinus opacification on CT scan. Patient selection criteria were chosen to ensure that the study population is generalizable to a broad population with CRS with adequate disease severity to allow for treatment effects to be detected. Additional prespecified endpoints of clinical importance included frequency of acute exacerbations, health-related quality of life, study-defined surgical eligibility, and health utility. Details of CT measures will be presented.

Conclusions: Thoughtful preparation, input from FDA, and applying an iterative process yielded a novel study design for testing CRS therapies.

F2

Indirect comparison of dupilumab versus tezepelumab in patients with severe asthma

Kenneth R Chapman, Patricia Guyot, François Bourhis, Jerome Msihid, Radhika Nair, Arpita Nag, Megan Hardin, Juby Jacob-Nara

Introduction: Dupilumab has demonstrated efficacy in patients with type 2 inflammation (blood eosinophils[EOS]≥150cells/µL or fractional exhaled nitric oxide[FeNO]≥25ppb). Tezepelumab has demonstrated efficacy in patients with severe asthma and ≥2 prior exacerbations. This indirect treatment comparison (ITC) assessed relative efficacy of dupilumab versus tezepelumab among patients with severe asthma.

Methods: We identified four double-blind, randomized trials investigating dupilumab (DRI[NCT01854047]; QUEST[NCT02414854]) or tezepelumab (PATHWAY[NCT02054130]; NAVIGATOR[NCT03347279]). Inclusion criteria were comparable except for prior annualized exacerbation frequency (≥1 in DRI and QUEST; ≥2 in NAVIGATOR; ≥2 needing systemic glucocorticoid/1 severe exacerbation leading to hospitalization in PATHWAY). We selected studies with similar definitions of prior exacerbation frequency (NAVIGATOR, QUEST, DRI) and selected populations with similar exacerbation frequency (≥2 in previous year). Bucher ITC was used to compare pooled dupilumab 200/300mg every 2 weeks with tezepelumab 210mg every 4 weeks. We evaluated following endpoints in the overall population and subgroups by baseline EOS and FeNO: annualized asthma exacerbation rate (AAER), pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV$_1$) at Week 24 (W24) and 52 (W52), and serum immunoglobulin E (IgE) at W52.

Results: Patient characteristics were comparable except for OCS use at baseline (dupilumab trials, none; NAVIGATOR, 9%). Dupilumab showed numerically lower AAER versus tezepelumab (rate ratio [95%CI], 0.97 [0.75 to 1.27]); a similar trend was observed across EOS≥150cells/µL, and FeNO≥25ppb subgroups. Improvement in pre-BD FEV$_1$ was significantly greater for dupilumab versus tezepelumab at W24 (mean difference [95%CI], 0.08L [0.02 to 0.14]); numerically greater at W52 in overall (0.06L [–0.01 to 0.14]) and EOS≥150cells/µL subgroup. Decreases in serum IgE at W52 were significantly greater with dupilumab than tezepelumab (–128.83IU/mL [–250.89 to –6.78]).

Conclusion: In patients with ≥2 exacerbations in previous year, dupilumab may lead to greater magnitude of clinical response including exacerbation reduction, lung function improvement, and suppression of IgE, versus tezepelumab.

F3

The Study Design of a Trial of Dupilumab in Adult Patients With Bullous Pemphigoid: LIBERTY-BP ADEPT

Dedee F. Murrell, Pascal Joly, Victoria P. Werth, Elizabeth Laws, Leda P. Mannent, Bethany Beazley, Ariane Dubost-Brama, Arsalan Shabbir

Introduction: The LIBERTY-BP ADEPT trial (NCT04206553) aims to investigate the efficacy and safety of dupilumab in achieving sustained remission off oral corticosteroids (OCS) in patients with moderate-to-severe bullous pemphigoid (BP).

Methods: LIBERTY-BP ADEPT is a global, randomized, double-blind, placebo-controlled, parallel-group study consisting of a 35-day screening period, a 52-week double-blind treatment period (dupilumab loading dose administered subcutaneously [SC] followed by SC dosing every 2 weeks [q2w] or matching placebo), and a 12-week follow-up period. Patients receive standard OCS to control disease activity at the start of the treatment period. After 2 weeks of sustained remission, OCS is to be gradually tapered and discontinued as long as disease control is maintained. The primary endpoint is the proportion of patients achieving sustained remission at Week 36.

Results: LIBERTY-BP ADEPT enrollment is ongoing and will include approximately 90% patients from Europe and the USA.

Conclusions: BP shares pathophysiological pathways with type 2 inflammatory diseases mediated by IL-4 and IL-13. The ongoing LIBERTY-BP ADEPT study is the first randomized, controlled trial designed to evaluate the efficacy and safety of dupilumab in patients with moderate-to-severe BP.

F4

Effect of Allergy Specialty Care on Healthcare Utilization Among Children with Peanut Allergy in the US

Matt Greenhawt, Elissa Abrams, Joseph M. Chalil, Todd D. Green, Marcus Shaker

Introduction/Rationale: The influence and cost of allergist management on peanut allergy (PA)-related healthcare utilization is unknown.

Methods: IBM MarketScan® Commercial Claims and Encounters Database was analyzed for PA diagnosis/reaction-related codes (January 2010-June 2019) in patients ≤64 years, with age cohort-matched non-PA food allergy controls (NPAFAC). Outcomes were measured and compared (t-tests/chi-square tests) 12 months pre/post first claim date.

Results: Among 72,854 PA-persons (39,068 with ≥1 allergist visit, 53.6%), and 166,825 age-matched NPAFAC, number of National Drug Codes (NDC) and ICD-10 codes were higher for PA-persons with vs. without an allergist visit during both baseline and follow-up (all p<0.001). PA-persons with an allergist visit vs. those without were prescribed epinephrine at a significantly higher rate (RR 1.67, p<0.001). Rates of epinephrine claims, mean epinephrine costs, and proportion with peanut anaphylaxis episodes were higher among the PA-group with vs. without an allergist visit (69.9% vs. 63.3%; $676 vs. $493, 48.9% vs. 20.7%; all p<0.001). The proportion with anaphylaxis episodes was higher in the PA vs NPAFAC group (53.1% vs. 31.6%, p<0.001). Total healthcare costs were higher in the NPAFAC vs. PA-group ($7,863 vs. $7,261, p<0.001), and lower for PA-persons with vs. without an allergist visit ($6,347 vs. $8,270, p<0.001), with no significant differences in PA reaction-related costs between PA groups.

Conclusion: Higher rates of anaphylaxis were seen among the PA-group with an allergist visit recorded during the follow-up period (53.6% of overall PA group) compared to those without. Allergist care was associated with a reduction in total healthcare costs and higher rates of epinephrine prescription.

Pooled Safety Data from Phase 3 Studies of Epicutaneous Immunotherapy for Peanut Allergy in Children Aged 4-11 Years

Rachel Robison, Jacqueline A. Pongracic, J. Andrew Bird, Amy M. Scurlock, Katharine J. Bee, Dianne E. Campbell, Jonas Meney, Aurélie Peillon, Hugh A. Sampson, David M. Fleischer

Introduction/Rationale: Epicutaneous immunotherapy with Viaskin Peanut 250 µg (VP250) has been studied in phase 3 clinical trials: PEPITES, a 12-month, randomized double-blind controlled trial (RDBCT) with an open-label extension (PEOPLE) and REALISE, a 6-month RDBCT followed by an open-label extension. We present pooled safety study data from subjects who received up to 36 months of VP250 treatment.

Methods: Analyses were performed on PEPITES, PEOPLE and REALISE databases. REALISE placebo subjects who received VP250 after the 6-month RDBC period were included in the pooled VP250 analysis. Adverse event outcomes included treatment-emergent adverse events (TEAEs), serious TEAEs, local cutaneous reactions and systemic allergic TEAEs considered VP250-related.

Results: 630 subjects received up to 36 months of VP250 treatment (1689.3 subject years [SY]) and 217 received placebo (164.8 SY). TEAEs occurred in 98.4% and 89.4% of subjects receiving VP250 and placebo, respectively; with 758.5 events per 100 SY in subjects under VP250 and 748.9 events per 100 SY in those receiving placebo. For VP250 subjects, the most common treatment-related TEAEs were administration site reactions (224.5 per 100 SY); anaphylactic reactions occurred at 3.7 events per 100 SY, and TEAEs treated with epinephrine occurred at 4.4 per 100 SY. Treatment-related TEAEs during VP250 administration were lower in the third year of treatment compared to years 1 and 2.

Conclusions: Pooled data from large (N=630), multicenter phase 3 clinical trials demonstrated treatment with VP250 for up to 36 months in peanut-allergic children was generally safe and well-tolerated. The most common treatment-related TEAEs were local skin reactions.

Dupilumab treatment restores skin barrier function and improves clinical and patient reported outcomes in adults and adolescents with moderate to severe atopic dermatitis

Robert Bissonnette MD, Inoncent Agueusop, Amy Praestgaard MS, Noah A. Levit MD, Ana B. Rossi MD, Annie Zhang MD

Objective: To determine the effect of dupilumab on skin barrier function in adults and adolescents with moderate to severe atopic dermatitis (AD).

Methods: Transepidermal water loss (TEWL) was measured before and after skin tape stripping (STS) in AD lesional skin (n=26) over 16 weeks of dupilumab therapy, and matched healthy control skin (n=26) in an Open Label Exploratory study (BALISTAD [NCT04447417]). TEWL before and after STS was assessed repeatedly between baseline and Week 16. Change from baseline in TEWL was analyzed using a mixed model, adjusting for age, gender, and lesion location. Secondary and exploratory endpoints included clinical, and patient reported outcomes. Photographic documentation was also obtained during the study.

Results: The mean TEWL in AD lesions was significantly reduced from baseline, (both before STS and following 5/10/15/20 STS) ranging from 47.2, 62.5, 73.0, 80.4, and 88.0 g/m^2 x h at baseline to 23.6, 28.3, 34.3, 42.9, and 49.2 g/m^2 x h at Week 16, respectively; representing 48% to 57% reduction (p<0.0001). By week 16, the mean distribution of TEWL in AD patients was close to matched healthy controls. Clinical and patient reported outcomes (EASI, SCORAD, peak pruritus NRS, sleep quality NRS, POEM and DLQI/CDLQI) significantly improved from baseline (p<0.0001 for all endpoints except CDLQI [p<0.01]).

Conclusions: Dupilumab treatment leads to significant improvement in TEWL in AD lesional skin, demonstrating restoration of epidermal barrier function and improvement in signs and symptoms of AD.

Family Impact of Moderate-to-Severe Atopic Dermatitis in Children Aged <12 years: Results From 732 Patients in the PEDIatric STudy in Atopic Dermatitis (PEDISTAD) Observational Study

Marjolein de Bruin-Weller, Marie L.A. Schuttelaar, Charles W. Lynde, Nelson Augusto Rosario Filho, Annie Zhang, Brad Shumel

Introduction & Objectives: To describe the real-world family impact of moderate-to-severe atopic dermatitis (AD) in children aged <12 years.

Materials & Methods: PEDISTAD (NCT03687359) is an ongoing, international, non-interventional study in patients aged <12 years with moderate-to-severe AD inadequately controlled with topical therapies or for whom such therapies are inadvisable. Baseline measures of disease severity reported include Eczema Area and Severity Index (EASI; 0–72) and AD-affected body surface area (BSA). Family impact measures used include Caregiver Global Assessment of Disease (CGAD) and Dermatitis Family Impact (DFI) questionnaire (10 questions, each scored 0 [not at all] to 3 [very much]; 0–30).

Results: Among 732 children (52.2% male; mean±SD age 6.2±3.2 years), EASI (mean±SD) was 14.4±10.7 and BSA affected (%), 33.3±21.0. Proportion of caregivers reporting no symptoms/mild, moderate and severe/very severe in CGAD were 24.2%, 42.2%, and 33.6%, respectively. Overall DFI (mean±SD) score was 10.9±7.4, with many caregivers reporting their child's AD had "very much"/"quite a lot" of impact on: expenditure (46.7%), tiredness/exhaustion (40.7%), family sleep (40.7%), caregiver life due to AD treatment (38.3%), emotional distress (37.5%), housework (32.6%), family leisure (25.9%), food preparation/feeding (23.3%), and family relationships (18.4%). Overall DFI scores worsened with increasing AD severity (by EASI/BSA). Results were comparable across age groups (0 to <2, 2 to <6, 6 to <12 years).

Conclusions: Caregivers of children with moderate-to-severe AD in PEDISTAD reported a multidimensional impact on caregiver/family life. Family impact also worsened with increasing AD severity. The impacts on caregivers/family should be considered when making treatment decisions for childhood moderate-to-severe AD.

Dupilumab Provides Long-Term Improvement in Sleep Loss in Children, Adolescents, and Adults With Atopic Dermatitis

Mette Deleuran, Eric L. Simpson, Amy Praestgaard, Haixin Zhang, Zhixiao Wang, Ana B. Rossi

Background: Atopic dermatitis (AD) is associated with impaired sleep quality. We evaluated the efficacy of dupilumab treatment on sleep up to 1 year in adults and adolescents with moderate-to-severe AD and children with severe AD.

Methods: We included 73 adolescents (aged 12–17 years) with moderate-to-severe AD (NCT03054428) and 110 children (aged 6–11 years) with severe AD (NCT03345914) who were treated for 16 weeks with FDA-approved dupilumab dose regimens in a double blind randomized placebo-controlled trial (children received concomitant medium-potency topical corticosteroids), and subsequently entered the LIBERTY AD PED OLE open-label extension study (NCT02612454) and were treated with dupilumab 300 mg q4w for up to 1 year (1Y; adolescents/children = 48 weeks; adults = 52 weeks). We also included 80 adults with moderate-to-severe AD who were optimal responders to dupilumab 300 mg q2w at Week 16 of LIBERTY AD SOLO 1/2 (NCT02277743/NCT02277769) and continued dupilumab monotherapy in the LIBERTY AD SOLO-CONTINUE (NCT02395133) for an additional 36 weeks

Results: Patients in all age groups reported sustained improvement in sleep following dupilumab treatment for up to 1 year. Adults had a mean baseline sleep loss Visual Analogue Scale score (range: 0 [no sleeplessness]–10 [worst imaginable sleeplessness]; recall period 3 days/nights) of 5.2, decreasing to 0.9 at Week 16, and 1.1 at 1Y. Adolescents had mean scores of 5.3 at baseline, 2.0 at Week 16, and 1.3 at 1Y. Mean scores for children <30kg were 6.7 at baseline, 2.1 at Week 16, and 1.5 at 1Y; and for children ≥30kg were 5.4 at baseline, 1.3 at Week 16, and 1.4 at 1Y. Overall safety was consistent with the known dupilumab safety profile.

Conclusion: Dupilumab treatment up to 1 year provided sustained improvement in sleep loss in children with severe AD, and adolescents and adults with moderate-to-severe AD.

Long-Term Safety Data for Dupilumab up to 4 Years in an Open-Label Extension Study of Adults With Moderate-to-Severe Atopic Dermatitis

Melinda Gooderham, Andreas Wollenberg, Weily Soong, Robert Bissonnette, Jing Xiao, Faisal A. Khokhar, Ainara Rodríguez Marco, Noah A. Levit, Arsalan Shabbir

Purpose: This analysis extends the dupilumab safety profile in moderate-to-severe atopic dermatitis (AD) patients from an open-label (OLE) extension study (NCT01949311) to 204 weeks.

Methods: Adults with moderate-to-severe AD who participated in any dupilumab parent study were enrolled (initial duration of 3 and up to 5 years). Following protocol amendments in 2017/2018, 114/272 patients re-entered the trial, and 103/207 patients had treatment interruption >8 weeks. Patients received 300mg dupilumab weekly and transitioned to the approved 300mg every 2 weeks dose in 2019. Concomitant topical treatments were permitted. Data shown for the overall study population (N=2,677).

Results: 2,207/1,065/557/362/352/240 patients completed 52/100/148/172/204/>204 weeks of treatment. 59.5% of withdrawals were due to dupilumab approval; 8.4% due to adverse events (AEs); 4.3% due to lack of efficacy. Exposure-adjusted incidence rates of treatment-emergent AEs (TEAEs) were lower vs 300mg qw+TCS arm of CHRONOS (167.5 vs 322.4 nP/100PY). 10.4% of patients had ≥1 serious TEAEs; 9.8%, ≥1 severe TEAEs; 1.2%, ≥1 serious TEAE related to study drug; 3.7%, ≥1 TEAEs resulting in treatment discontinuation. Most common TEAEs were nasopharyngitis (28.9%) and conjunctivitis (20.0%).

Conclusions: This OLE study in adults with moderate-to-severe AD extends the reported dupilumab safety profile to 4 years.

Efficacy and Safety of Dupilumab in Children Aged ≥6 Months to <6 Years With Moderate-to-Severe Atopic Dermatitis

Amy S. Paller, Elaine C. Siegfried, Eric L. Simpson, Andreas Wollenberg, Mercedes E. Gonzalez, Robert Sidbury, Benjamin Lockshin, Jing Xiao, John T. O'Malley, Ashish Bansal

Background: There is a high unmet medical need in pediatric patients aged 6 months to <6 years with moderate-to-severe atopic dermatitis (AD). We present pivotal phase 3 efficacy and safety data of dupilumab in children aged 6 months to <6 years with moderate-to-severe AD.

Methods: In LIBERTY AD INFANTS/PRE-SCHOOL (NCT03346434 part B), a double-blind, placebo-controlled trial, children aged 6 months to <6 years with moderate-to-severe AD inadequately controlled with topical therapies were randomized 1:1 to subcutaneous dupilumab every 4 weeks (q4w) (baseline weight ≥5–<15kg: 200mg; ≥15–<30kg: 300mg) or placebo for 16 weeks. From Day –14, all patients initiated standardized treatment with low-potency topical corticosteroids (TCS).

Results: 162 patients were randomized (dupilumab/placebo groups, n=83/79); 157 (96.9%; dupilumab/placebo n=82/75) completed 16 weeks of treatment. At Week 16, 27.7%/3.9% ($P<0.0001$) of patients receiving dupilumab/placebo achieved an IGA score of 0–1 (clear/almost clear), and 53.0%/10.7% ($P<0.0001$) achieved ≥75% improvement in Eczema Area and Severity Index (EASI). Least squares (standard error) mean percent change from baseline at Week 16 in EASI and weekly averaged worst scratch/itch score in dupilumab/placebo was –70.0%(4.9)/–19.6%(5.1) ($P<0.0001$) and –49.4%(5.0)/–2.2%(5.2) ($P<0.0001$), respectively. Improvements were statistically significant by Week 4. In dupilumab/placebo groups, treatment-emergent adverse events (TEAE), serious TEAE and TEAE-related treatment discontinuation were reported in 63.9%/74.4%, 0%/5.1% and 1.2%/1.3% of patients, respectively. Incidence of conjunctivitis (narrow cluster) and skin infection was 4.8%/0% and 12.0%/24.4%, respectively. Most common TEAEs were dermatitis atopic (13.3%/32.1%), nasopharyngitis (8.4%/9.0%), upper respiratory tract infection (6.0%/7.7%), impetigo (3.6%/7.7%), and lymphadenopathy (3.6%/7.7%).

Conclusions: In children (6 months to <6 years) with moderate-to-severe AD, dupilumab q4w+TCS vs placebo+TCS rapidly and significantly improved AD signs and symptoms. Dupilumab was well tolerated with a favorable safety profile.

Annual Inhaled Corticosteroid, Short-acting Beta₂-Agonist and Systemic Corticosteroid Exposure in Adolescents and Adults with Asthma in the United States

Miguel Lanz, Ileen Gilbert, Michael Pollack, Hitesh Gandhi, Joseph Tkacz

Rationale: The Global Initiative for Asthma (2021) and National Asthma Education and Prevention Program (2020) recommend concomitant fast-acting bronchodilators and inhaled corticosteroids (ICS) for rescue therapy in patients ≥12 years, as this approach can reduce exacerbations requiring systemic corticosteroids (SCS). We assessed ICS, short-acting beta₂-agonist (SABA), and SCS exposures and compared the relative magnitude of observed SCS versus projected ICS that could occur if as-needed SABA were combined with ICS.

Methods: IBM® MarketScan® databases of 2010–2017 administrative claims for US patients ≥12 years receiving SABA for asthma were evaluated. Patients were indexed on a random SABA claim, had 12-months' continuous eligibility pre- and post-index, and filled post-index ICS-based maintenance medication totaling >32 days' supply or ≥1 additional SABA if no maintenance. Post-index ICS (μg/day fluticasone propionate [FP] equivalents), SABA (inhalations/day based on 200 inhalations/canister) and SCS (mg/year prednisone equivalents) were analyzed, assuming full claims use. As budesonide is the most-studied rescue ICS, projected as-needed ICS over the post-index year was calculated assuming each SABA inhalation contained 80 μg budesonide (50 μg FP equivalent). Maximum acceptable daily ICS ranges were derived from FDA-approved FP product labels. Statistics were descriptive and unadjusted.

Results: 577,394 patients were identified. 63% filled SABA only (41% with SCS exposure); 37% filled ICS-based maintenance (40% with SCS). For each maintenance therapy, mean post-index ICS μg/day was below the respective maximum approved levels, ranging from 24% (high-dose ICS/long-acting beta₂-agonist [LABA]) to 52% (low-dose ICS) of FDA approved daily doses. Mean (standard deviation) post-index SABA ranged from 2.2 (2.2) canisters (~1.2 inhalations/day, SABA only group) to 4.9 (4.8) canisters (~2.7 inhalations/day, ICS/LABA/long-acting muscarinic antagonist [LAMA] group). If each SABA inhalation was combined with 80 μg budesonide, total projected maintenance plus as-needed ICS/day would range from 36% (high-dose ICS/LABA) to 100% (low-dose ICS) of respective approved doses. For all groups, mean post-index SCS exposure exceeded 500 mg/year prednisone equivalents, ranging from 542 (1,438) mg (low-dose ICS/LABA) to 1,088 (2,148) mg (ICS/LABA/LAMA). Total annual projected mgs of ICS were 6.2 (medium/high dose ICS) to 28.0 (SABA only) times lower than mgs of observed SCS exposure.

Conclusions: Many patients ≥12 years with asthma have SCS exposures associated with the development of adverse health conditions (≥500 mg). Even if as-needed SABA with concomitant ICS remains at the same level as current SABA use, modeled ICS exposure is within the range of approved doses and patients could benefit from reduced SCS exposures.

Tezepelumab Reduces Exacerbations Across All Seasons in Patients with Severe, Uncontrolled Asthma: Results from the Phase 3 NAVIGATOR Study

Flavia Hoyte, Neil Martin, Kamil Kmita, Stephanie Roseti, Jean-Pierre Llanos-Ackert, Andrew Lindsley and Gene Colice

Introduction: Tezepelumab is a human monoclonal antibody that targets thymic stromal lymphopoietin (TSLP). The phase 3 NAVIGATOR study (NCT03347279) investigated the efficacy and safety of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Seasonal variations in the frequency of asthma exacerbations can occur owing to the presence of different exacerbation triggers (e.g. allergens and viruses) during different seasons. This prespecified exploratory analysis evaluated the effect of tezepelumab on asthma exacerbations across all seasons in patients from NAVIGATOR.

Methods: NAVIGATOR was a multicenter, randomized, double-blind, placebo-controlled study. Patients (12-80 years old) were randomized 1:1 to receive tezepelumab 210 mg or placebo subcutaneously every 4 weeks for 52 weeks. The annualized asthma exacerbation rate (AAER) and the proportion of patients without exacerbations were assessed by season. Data from patients in the Southern Hemisphere were transformed to align with Northern Hemisphere seasons.

Results: Of 1059 treated patients, 528 received tezepelumab 210 mg and 531 received placebo. Compared with placebo, tezepelumab reduced the AAER by 63% (95% CI, 52-72) in winter, 46% (95% CI, 26-61) in spring, 62% (95% CI, 48-73) in summer and 54% (95% CI, 41-64) in fall. The proportion of patients without exacerbations was higher in the tezepelumab group than in the placebo group in winter (81.7% vs 66.6%), spring (84.3% vs 76.3%), summer (86.8% vs 73.1%) and fall (79.4% vs 66.6%).

Conclusions: In adults and adolescents with severe, uncontrolled asthma, treatment with tezepelumab consistently reduced exacerbations across all seasons compared with placebo.

CAPTAIN: Relationship between FEV$_1$ reversibility at screening as a continuous variable and treatment response

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Introduction: In patients with uncontrolled asthma despite ICS/LABA, the effects of adding LAMA or increasing ICS may vary by FEV$_1$ reversibility. CAPTAIN showed that adding the LAMA umeclidinium (UMEC) to the ICS/LABA combination of fluticasone furoate/vilanterol (FF/VI) improved lung function and symptom control. We therefore investigated whether FEV$_1$ reversibility at screening predicts the response to adding UMEC or increasing FF dose.

Methods: CAPTAIN was a Phase IIIA, randomized, double-blind, 24–52-week, parallel-group study in adults with uncontrolled asthma despite ICS/LABA and airflow reversibility at screening (FEV$_1$ increase $\geq$12% and $\geq$200mL, 20–60 minutes after four inhalations of albuterol/salbutamol). Treatment: FF/VI (100/25, 200/25mcg) or FF/UMEC/VI (100/31.25/25, 100/62.5/25, 200/31.25/25, 200/62.5/25mcg) once-daily. Outcomes: change from baseline in trough FEV$_1$ (Week 24; post-hoc analysis using mixed-model repeated measures) and annualized moderate/severe exacerbation rate (Weeks 1–52; post-hoc analysis using a negative binomial model) by FEV$_1$ reversibility at screening. Treatment groups were pooled by addition of UMEC 62.5mcg or FF dose. For fractional polynomial modeling, models were adjusted for two fractional polynomial transformations of reversibility at screening and their interactions with treatment.

Results: Across the range of reversibility at screening, numerically greater improvements in trough FEV$_1$ were seen with adding UMEC; improvements were also observed from increasing FF dose, although there was substantial overlap in the 95% CIs. Increasing FF dose led to numerical reductions in exacerbation rate across the range of reversibility, although there was some overlap in CIs, particularly at the extremes of reversibility due to lower patient numbers; adding UMEC had minimal impact.

Conclusions: Improvements in lung function were largely independent of FEV$_1$ reversibility at screening, with greater improvements observed following UMEC addition. Increasing FF dose led to a reduction in moderate/severe exacerbation rates independently of FEV$_1$ reversibility at screening, whereas adding UMEC had a minimal effect.

CAPTAIN: Effects of asthma onset in childhood versus adulthood on response to triple therapy in patients with inadequately controlled asthma on inhaled corticosteroid/long-acting β$_2$-agonist

Busse W, Abbott CB, Chang S, Crawford J, Maselli DJ, Nathan R, Stanaland MD, Kerwin E

Introduction: CAPTAIN showed that adding umeclidinium (UMEC) to fluticasone furoate/vilanterol (FF/VI) improved lung function and symptom control in uncontrolled asthma. As response to inhaled therapy may vary according to the age at which a patient develops asthma, we evaluated CAPTAIN treatment outcomes in patient subgroups defined by age of asthma onset.

Methods: This Phase IIIA, double-blind, 24–52-week, parallel-group study randomized adults ($\geq$18 years) with uncontrolled asthma on ICS/LABA. Treatment: once-daily FF/VI (100/25, 200/25mcg) or FF/UMEC/VI (100/31.25/25, 100/62.5/25, 200/31.25/25, 200/62.5/25mcg). Outcomes: change from baseline in FEV$_1$ (Week 24); annualized rate of moderate/severe exacerbations (Weeks 1–52); proportion of patients meeting responder threshold ($\geq$0.5-point decrease from baseline) in Asthma Control Questionnaire (ACQ)-7 score (Week 24) by age of asthma onset (<18 [childhood-onset, n=645] vs $\geq$18 years [adult-onset, n=1790]; post-hoc).

Results: Adding UMEC or increasing FF dose led to numerical improvements in FEV$_1$ in both subgroups, with more pronounced improvements following addition of UMEC to FF/VI 100/25mcg, increasing FF dose in FF/VI, or increasing FF dose and adding UMEC (simultaneous step-up) in the childhood- versus adult-onset subgroup. Adding UMEC and/or increasing FF dose led to decreases in moderate/severe exacerbation rate in the adult-onset subgroup. In the childhood-onset subgroup, adding UMEC to FF/VI 100/25mcg or increasing FF dose in FF/VI 100/25mcg led to decreases in moderate/severe exacerbation rate, whereas there was no clear effect from adding UMEC to FF/VI 200/25mcg, increasing FF dose in FF/UMEC/VI, or simultaneous step-up. All treatment strategies led to greater odds of ACQ-7 response in both subgroups, except for increasing FF dose in FF/UMEC/VI in the childhood-onset subgroup.

Conclusions: Adding UMEC and/or increasing FF dose was generally associated with improved lung function and greater odds of ACQ-7 response regardless of age of asthma onset, as well as reductions in exacerbation rates in patients with adult-onset asthma.

CAPTAIN study: Effects of baseline IgE levels on triple therapy response in inadequately controlled asthma

Oppenheimer J, Abbott C, Chang S, Chupp G, Crawford J, Mannino D, Win P

Introduction: CAPTAIN showed that adding umeclidinium (UMEC) to fluticasone furoate/vilanterol (FF/VI) improved lung function and symptom control in uncontrolled asthma; treatment response varied by baseline type-2 inflammatory biomarkers. As IgE may also influence response, we evaluated the impact of adding UMEC and/or increasing FF dose according to baseline IgE levels.

Methods: This Phase IIIA, double-blind, 24–52-week study randomized adults with uncontrolled asthma despite ICS/LABA. Treatment: once-daily FF/VI (100/25, 200/25mcg) or FF/UMEC/VI (100/31.25/25, 100/62.5/25, 200/31.25/25, 200/62.5/25mcg). Outcomes: change from baseline in trough forced expiratory volume in 1 second (FEV$_1$; Week 24); annualized rate of moderate/severe asthma exacerbations (Weeks 1–52); Asthma Control Questionnaire (ACQ)-7 response ($\geq$0.5-point decrease from baseline; Week 24) by baseline IgE: $\leq$85 (n=801), >85–$\leq$306 (n=803), >306 KU/L (n=803) (post-hoc).

Results: Numerical improvements from baseline in trough FEV$_1$ were observed following addition of UMEC regardless of baseline IgE levels (difference [95% CI]) in FEV$_1$ for $\leq$85, >85–$\leq$306 and >306 KU/L, respectively: 141mL [65, 217], 134mL [56, 212], 52mL [-21, 125] for FF/UMEC/VI 100/62.5/25 vs FF/VI 100/25; 77mL [4, 151], 113 [38, 187], 87mL [8, 166] for FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25); increasing FF dose generally had a lesser effect. Less consistent effects were seen on moderate/severe exacerbations across IgE subgroups; however, in general, greater reductions in exacerbations were seen from doubling FF dose versus adding UMEC. Numerically greater odds of ACQ-7 response was also seen for all treatment strategies across all IgE subgroups, except doubling FF dose in triple therapy in the >306 KU/L subgroup.

Conclusions: Effects of adding UMEC and/or increasing FF dose according to IgE levels were generally consistent with the overall population. Although eosinophils and IgE levels are associated with type-2 inflammation, their influence on treatment response differs; unlike eosinophils, baseline IgE levels do not appear to predict treatment response.

Primary and Safety Outcomes of a Phase 3 Placebo-Controlled, Randomized Clinical Trial of PI3K

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Introduction: Phosphoinositide 3-kinase delta (PI3Kδ) is encoded by PIK3CD and PIK3R1, and pathogenic genetic variants causing kinase hyperactivity can result in a primary immune regulatory disorder known as activated PI3Kδ syndrome (APDS). Patients with APDS present with dysregulated B and T cells leading to immunodeficiency and immune dysregulation often manifesting as recurrent sinopulmonary and persistent herpesvirus infections, lymphoproliferation, autoimmunity, enteropathy, and increased risk of lymphoma. Current treatments are empirical. We previously reported use of molecularly targeted inhibition of hyperactive PI3Kδ signaling with the investigation drug leniolisib (CDZ173) in 6 patients withAPDS in a 12-week, open-label, within-subject dose-escalation Phase 2/3 clinical trial (Part 1 of NCT02435173; Rao VK, et al. Blood. 2017;130(21):2307-2316), as well as an interim analysis of the openlabel extension study (Rao VK, et al. Blood. 2018;132(suppl1):3706).

Methods: Here we report outcomes from a randomized 2:1, placebo-controlled, triple-blinded, fixed dose study (Part 2 of NCT02435173). Thirty-one patients aged $\geq$12 years were enrolled globally. Co-primary outcomes were: 1) change at 12 weeks from baseline in log10 transformed sum of product of diameters in the index lesions (lymph nodes) and 2) change from baseline in percentage of naïve B cells out of total B cells.

Results: At baseline, lymphadenopathy and chronic infection were nearly universal (93.5% and 90.3%, respectively). Both primary efficacy endpoints were met (p=0.0012 and p<0.0001, respectively). The majority of patients had APDS1 (80.6%). The median age was 21.0 years (range, 12-55 years) and 61.3% of patients were <22 years old. Leniolisib was well tolerated. No AEs led to discontinuation of study treatment. No serious AEs were suspected to be related to the investigational agent; 23.8% of leniolisib and 30.0% of placebo adverse events (AEs) were reported as related to study treatment.

Conclusion: Leniolisib was well tolerated and met both primary efficacy endpoints in patients with APDS.

Results of a Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study, Investigating the Safety and Efficacy of Anti-Factor XIIa Monoclonal Antibody Garadacimab (CSL312) for Prophylaxis of HAE

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Introduction: The activated factor XII (FXIIa)-driven contact pathway is essential for bradykinin production, a mediator of hereditary angioedema (HAE). Garadacimab (CSL312) is a fully human IgG4 monoclonal antibody that inhibits FXIIa. This Phase 2 study (CSL312_2001; NCT03712228) investigated the safety, efficacy, and pharmacokinetics of prophylactic subcutaneous (SC) garadacimab in HAE.

Methods: Eligible patients with type I/II HAE were randomized to receive placebo or 75, 200, or 600 mg SC garadacimab every 4 weeks for 12 weeks. One week prior to the first SC dose, an intravenous volume-matched loading dose of 0, 40, 100, or 300 mg was administered to the four groups, respectively. The primary endpoint was monthly HAE attack rate. Further endpoints included the reduction in attacks compared with the 4–8-week run-in or placebo, use of on-demand medication per month, and safety.

Results: Overall, 32 adult patients, with a mean monthly attack rate of 5.17 during the run-in period, were randomized; 56.25% were female, 90.63% were white, and 93.75% had type I HAE. The mean monthly attack rates were 4.24, 0.48, 0.05, and 0.40 for patients in the placebo, 75, 200, and 600 mg SC garadacimab arms, respectively. The mean percentage reduction in monthly attack rates in the garadacimab arms relative to placebo were 88.68%, 98.94%, and 90.50%. The percentage of patients experiencing at least one treatment-emergent adverse event (TEAE) with garadacimab was similar to placebo. All adverse events were non-serious and determined to be mild or moderate. The most common TEAE related to the treatment (garadacimab and placebo) was mild-to-moderate injection site erythema (12.5%). All patients completed the study.

Conclusions: Monthly prophylactic SC treatment with garadacimab was well tolerated and effective in preventing attacks in patients with HAE. This study provides the first clinical evidence for the role of this anti-FXIIa antibody in the management of HAE.

A Phase 1, Single-Center, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Intravenous and Subcutaneous Garadacimab (CSL312) in Healthy Subjects

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Introduction: Garadacimab is a fully human immunoglobulin G4 monoclonal antibody that inhibits activated factor XII (FXIIa). This Phase 1 study assessed the safety, tolerability, and pharmacokinetics (PK)/pharmacodynamics (PD) profile of single ascending doses of garadacimab in healthy volunteers.

Methods: Five intravenous (IV) cohorts (0.1, 0.3, 1, 3, or 10 mg/kg doses) and 3 subcutaneous (SC) cohorts (1, 3, or 10 mg/kg doses) were included, with matching placebo administered within each cohort. Safety follow-up lasted for 85 days after administration. Blood samples were collected throughout for PK/PD analysis.

Results: Forty-eight male subjects, mean age (standard deviation) 27.4 (6.4) years, were included. No deaths, serious treatment-emergent adverse events (TEAEs), or TEAEs leading to discontinuation were reported. The frequency and severity of TEAEs were not dose-dependent and no anti-drug antibodies were detected. Mean maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve from the time of dosing up to collection time t (AUC_{0-t}) increased in a dose-dependent manner (IV and SC). Median time to maximum concentration in plasma (t_{max}) was 1.0 hour (end of infusion) for four of the IV cohorts (3.5 hours for the 0.1 mg/kg dose) and 5.6–7.0 days for SC cohorts. Mean terminal elimination half-life ($t_{1/2}$) was 14.3–20.4 days and 18.2–19.6 days for the IV and SC doses, respectively. Absolute bioavailability after SC administration was 49.7%. Garadacimab IV and SC exhibited dose-dependent inhibition of FXIIa-mediated kallikrein activity with no or minimal residual activity at higher doses.

Conclusions: Single-dose garadacimab IV and SC was well tolerated in healthy male subjects. Dose-dependent increases in plasma concentration and pharmacodynamic effects in the kallikrein–kinin pathway were observed. These results informed the design of further investigations, including a Phase 2 study in hereditary angioedema.

Phase 3 trial design for KVD900, a novel investigational oral plasma kallikrein inhibitor for the on-demand treatment of hereditary angioedema attacks

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Introduction: A phase 3 clinical trial is underway for KVD900, a novel investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema (HAE) attacks.

Methods: The KONFIDENT phase 3 randomized, double-blind, placebo-controlled trial will evaluate the efficacy and safety of KVD900 in patients aged ≥12 years with HAE type I or II, including patients taking long-term prophylaxis with breakthrough attacks. At least 84 patients will treat 3 eligible attacks with placebo, 300mg, or 600mg KVD900 in a 3-way crossover trial, with a ≥48h washout period between attacks.

Results: The primary endpoint is the time to beginning of symptom relief, defined as a Patient Global Impression of Change (PGI-C) rating of at least "A Little Better" for 2 consecutive timepoints within 12h of study drug administration. Previous sensitivity, specificity, and agreement analysis using Cohen's kappa in a phase 2 trial of KVD900 demonstrated that PGI-C was a sensitive measure to identify the beginning of symptom relief, consistent with findings using Patient Global Impression of Severity (PGI-S) and a composite visual analog scale (VAS; abdominal pain, skin pain, and skin swelling). Secondary endpoints include time to first ≥1 level decrease from baseline in PGI-S rating within 12h, time to attack resolution (PGI-S rating of "None") within 24h, proportion of attacks with symptom relief (PGI-C rating of at least "A Little Better" for 2 timepoints) within 4 and 12h, time to PGI-C rating of at least "Better" within 12h, and time to ≥50% decrease in composite VAS for 3 consecutive timepoints within 12 and 24h. Safety measures include adverse event monitoring, laboratory tests, electrocardiogram, and physical examinations.

Conclusions: The KONFIDENT phase 3 trial will evaluate KVD900, an oral therapy for on-demand treatment of HAE attacks, providing data on efficacy and safety in a large population of adult and adolescent patients with HAE.

Oral KVD900 Provides Rapid Inhibition of Plasma Kallikrein and Fast Improvement in Attack Symptoms in Patients With Hereditary Angioedema

Michael D. Smith, Edward J. Duckworth, Sally L. Hampton, Christopher M. Yea, Paul Audhya, Edward P. Feener

Introduction: There is an unmet need for an oral on-demand therapy that provides fast symptom relief for people who experience attacks from hereditary angioedema (HAE). Here we present the pharmacokinetics (PK), pharmacodynamics (PD), and time to improvement of attack symptoms evaluated in a phase 2 trial of KVD900, a novel oral plasma kallikrein (PKa) inhibitor in development for the on-demand treatment of HAE attacks.

Methods: Adults with HAE type I or II received a single 600mg dose of KVD900 for PK and PD evaluation over 4h (42 patients). PKa activity was evaluated in dextran sulfate–stimulated plasma. Efficacy and safety of KVD900 to treat HAE attacks was assessed in a randomized, double-blind, placebo-controlled crossover trial (53 patients). Time to symptom relief was measured using the Patient Global Impression of Change ([PGI-C]; attack rated at least "A Little Better" for 2 consecutive timepoints within 12h). Time to improvement in symptoms and attack severity within 12h were measured using the composite visual analog scale ([VAS]; ≥50% reduction from baseline in composite VAS for 3 consecutive timepoints) and Patient Global Impression of Severity ([PGI-S]; improvement by ≥1 level), respectively. *P* values for time-to-event data were determined using Gehan's generalized Wilcoxon test.

Results: KVD900 was rapidly absorbed and provided near-complete inhibition of PKa activity in plasma within 15 minutes, which was maintained for at least 4h. KVD900 treatment was associated with significantly shorter time to symptom relief observed on the PGI-C scale within 12h (1.6h vs. 9.0h; *P*<0.0001), and improvements in composite VAS (6.0 vs. >12.0h; *P*<0.0001) and PGI-S (9.0 vs. >12.0h; *P*=0.0002) scores within 12h, compared with placebo.

Conclusions: Oral administration of KVD900 achieved rapid and near-complete PKa inhibition, which was associated with fast symptom relief in people with HAE.

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Agreement Between Improvements in Patient Global Impression of Change and Other Measures of Improvement and Attack Resolution Observed in a Phase 2 Trial With KVD900 in Patients With Hereditary Angioedema

Paul K. Audhya, Michael D. Smith, Peter Williams, Christopher M. Yea, Danny M. Cohn

Introduction: KVD900 is an investigational oral plasma kallikrein inhibitor for on-demand treatment of hereditary angioedema (HAE). This post hoc analysis from a randomized, double-blind, placebo-controlled, phase 2 trial assessed agreement between improvements on the Patient Global Impression of Change (PGI-C) scale and other measures of improvement and attack resolution in patients with HAE.

Methods: Adults with HAE type I or II treated up to 2 attacks with 600mg KVD900 or placebo. Improvement in PGI-C was defined as a rating of at least "A Little Better" for 2 consecutive timepoints or at least "Better" for 1 timepoint. Other measures of improvement included no use of rescue medication, ≥1 level reduction in PGI-Severity (PGI-S), and ≥50% reduction from baseline in composite visual analog scale (VAS). Measures of attack resolution were PGI-S rating of "None" and VAS score of <10mm for all VAS components for 3 consecutive timepoints. Cohen's kappa, sensitivity, and specificity between PGI-C and other measures were assessed within 24h of dosing.

Results: Sixty patients completed ≥1 attack treatment (n=113 attacks). PGI-C ratings of "A Little Better" (2 timepoints) and "Better" (1 timepoint) showed moderate to substantial agreement with improvements on PGI-S and VAS and with rescue medication use (Cohen's kappa: 0.53, 0.67, 0.49 and 0.70, 0.78, 0.60). Fair to substantial agreement was observed between PGI-C improvements and attack resolution. Across each comparison, PGI-C "A Little Better" showed higher sensitivity but somewhat lower specificity vs PGI-C "Better." 82.3% and 80.0% of attacks rated at least "A Little Better" within 4h and 12h were rated at least "Better" within 24h of dosing.

Conclusions: Improvements observed on PGI-C scale demonstrated agreement with other measures of improvement and attack resolution in the phase 2 trial of oral on-demand drug candidate KVD900, further validating PGI-C as a meaningful measure of efficacy in patients with HAE.

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Persistence of Asthma Biologic Use in Clinical Practice

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Introduction: Little is known about persistence of asthma biologic use in clinical practice. Current international asthma guidelines suggest a trial of asthma biologics for at least 4 months.

Methods: A cohort of people with asthma who used at least 1 asthma biologic was constructed using data from 2003-2019 in the OptumLabs Data Warehouse (OLDW). Treatment persistence was defined by the length of time that a person continuously used an asthma biologic, allowing for a lapse in use up to 4 months before confirming that a person stopped. Clinical response to treatment (defined as a decline in asthma exacerbations of at least 50% compared to the 6 months before starting an asthma biologic) was described over time and in relation to biologic persistence.

Results: There were 9,575 people who had at least 1 episode of asthma biologic use, of whom 6,216 had continuous insurance coverage for 6+ months. There were 2,986 people (48%, 95% CI: 47%, 49%) who completed ≥6 months on an asthma biologic and 1,519 (24%, 95% CI; 23%, 25%) who completed ≥ 12 months. Of people with ≥1 asthma exacerbation 6 months before index biologic use, 63%, 76%, 80% and 81% realized a ≥50% reduction in post-index asthma exacerbations in the first 6 months, 6-12 months, 12-24 months and 24+ months, respectively.

Conclusion: About half (48%) of people remained on an asthma biologic for ≥6 months after first use. Most people who achieved a reduction in asthma exacerbations did so in the first 6 months of treatment.

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Asthma Severity And Risk For Cardiac Dysrhythmias

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INTRODUCTION: Previous studies have shown an increased risk for cardiac dysrhythmias (dysrhythmias) in patients with persistent asthma. No prior studies have examined the relationship between asthma severity classifications (ICD-10) and the risk for dysrhythmias.

METHODS: The study included a 100% sample of the Colorado All Payers Data set from 1/2017 to 6/2020. Asthma and Dysrhythmias were based on AHRQ's CCS grouping systems for ICD diagnostic codes. Asthma severity was classified as Mild, Moderate, or Severe Persistent (ICD10 nomenclature). Cough and exercise asthma were classified as Mild persistent. Logistic regression analysis was used to predict the association between Asthma, asthma severity subgroups and dysrhythmias. Results were reported as Odds Ratios (OR).

RESULTS: Our study included 3,841,761 patients (ages 0-65+,54% female) with 209,351 patients having a diagnosis of asthma. Controlled for age and sex, the association between preexisting asthma and a diagnosis of dysrhythmia was as follows : OR 1.822 (1.768, 1.878) P (<0.0001). Associations as per subgroups of asthma severity were as follows: Mild- OR 1.326 (1.275, 1.378) P (<0.0001); Moderate- OR 1.994 (1.903, 2.091) P (<0.0001); Severe- OR 3.309 (3.070,3.567) P (<0.0001).

CONCLUSIONS: In our large sample, a diagnosis of asthma was associated with increased risk for cardiac dysrhythmias. Furthermore, we found a linear correlation between asthma severity classification and risk for cardiac dysrhythmias. Patients with more severe asthma should be monitored closely for cardiac dysrhythmias.

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Autoimmune Disease Burden in Patients with Chronic Spontaneous Urticaria: A Nationwide Longitudinal Study.

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Introduction: Chronic Spontaneous Urticaria (CSU) affects 0.5–1% of the population. In this retrospective multicenter study, we investigated the incidence and risk factors for comorbid autoimmune diseases (AID) using Cerner Health Facts, a national longitudinal database representing approximately 69 million patients.

Methods: We defined a diagnosis of CSU as (1) two outpatient diagnoses of idiopathic urticaria, other specified urticaria, or urticaria, unspecified at least 6 weeks apart; or (2) one outpatient diagnosis of aforesaid urticaria plus one diagnosis of angioneurotic edema at least 6 weeks apart. All patients 18 years of age or older with CSU were included. Patient characteristics were evaluated as potential risk factors for AID comorbidity using multivariable regression built using all variables with p<0.1 on univariable analysis.

Results: We identified 6,704 patients with CSU. Mean age was 46.74±17.15 years, 74.43% (4990) were female, and 10.92% (732) were obese. In terms of race, 62.59% (4,196) were white and 19.42% (1,302) were African American. Overall, 18.38% (1232) of patients with CSU had at least one comorbid AID. The most common AID was autoimmune thyroid disease. On multivariable regression, the factors associated with higher risk of AID included female sex (odds ratio (OR) 2.80), long-term medication use (OR 1.81), depression (OR 1.43) and anxiety (OR 1.34), obesity (OR 1.25), hyperlipidemia (OR 1.30), type 2 diabetes (OR 1.23), digestive disorders (OR 1.21), and hypertension (OR 1.20). African American (OR 0.71; 95%CI 0.59-0.85), and other race (OR 0.78; 0.65-0.93) decreased the risk of comorbid AID.

Conclusions We utilized a national database of patients with diagnosed CSU to identify the incidence and risk factors for comorbid AID. Female sex was the greatest risk factor for comorbid AID, followed by depression and anxiety. Given that nearly 20% of identified CSU patients had comorbid AID, careful consideration and evaluation for AID in patients with CSU is advised.

Pooled Analysis of Headache and Migraine Incidence in Gammaplex 5% and 10% in Patients with Primary Immunodeficiency

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Introduction: Intravenous immune globulin (IVIG) infusions are administered across a broad range of infusion rates depending on the brand, labeling, and tolerability. Three pivotal studies support the efficacy, safety, and tolerability of a branded IVIG product in adults and children with primary immunodeficiency (PI). The purpose of this pooled analysis is to review the rates of headache and migraine across these clinical studies.

Methods: Infusion and tolerability data from three Gammaplex studies in PI were collected and pooled. In these studies, a unique infusion rate ramp-up protocol was utilized that increased every 15 minutes to a maximum rate of 8 mg/kg/min. Infusion summaries were generated to identify the proportion of infusions reaching the maximum infusion rate. Summaries of tolerability were generated to identify product-related headaches and migraines.

Results: In the pooled analysis, 94.6% of infusions reached the maximum infusion rate. Of the total infusions, 6.1% were associated with headaches and 0.5% with migraines. The overall rates of headaches and migraines as a function of total number of infusions were 7.1% and 0.6%, respectively, in adults receiving the 5% or 10% formulation and 3.9% (headaches) and 0.2% (migraines) in pediatrics receiving either formulation. The overall rates of headache and migraine by product formulation were also analyzed.

Conclusion: Adverse events such as headache and migraine have been reported with IVIG and in some cases may be related to infusion rate, a key determinant of overall infusion time for IVIG. Analyses of the occurrence of headache and migraine showed consistently low rates when compared by gender, age ranges, and percent achieving maximum infusion rate. Both the 5% and 10% formulations of this IVIG product were associated with a low rate of headache and migraine across various points of comparison in patients with PI when utilizing a 15- minute ramp-up infusion protocol.

An Interesting Case of Common Variable Immunodeficiency Disease

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Background: Common variable immunodeficiency (CVID) is a primary immunodeficiency characterized by impaired B cell differentiation leading to significant hypogammaglobulinemia with incidence of 1:25,000 persons. Underlying etiologies are poorly understood, however, 10% of cases are via genetic mutations. Most prevalently, NFKB 1, a transcriptional regulation gene responsible for immunological response to infections.

Objective: We present a case of adulthood diagnosis of CVID in a patient with mild history of childhood sinus infections reoccurring briefly in adulthood, found to have remarkably low immunoglobulin levels on serum testing prompting genetic sequencing with resultant of NFKB 1 mutation.

Case: A 32 year old patient presented to our clinic due to ongoing sinus infections. Medical history revealed few sinus infections per year in childhood requiring antibiotics, shingles at age 18 and 25, HPV age 16, and cervical carcinoma. In adulthood, continued with worsening sinus infections requiring sinus surgery. Surgical history included tonsillectomy and adenectomy. Family history revealed mother with unknown immunological disorder complicated by bilateral full lung transplant with death at age 44. Physical exam and imaging were unremarkable.

On initial laboratory testing, immunological findings showed markedly decreased serum immunoglobulins - IgA <5 mg/dL, IgM <5 mg/dL, IgE < 2IU/mL, and IgG 38 mg/dL. Tetanus and diphtheria toxoid IgG were 0.14 IU/mL and <0.1 respectively. Laboratory findings in conjunction with patient history were consistent with CVID. Lymphocyte subset panel, mitogen response to phytohemagglutinin pokeweed and Staphylococcal enterotoxin B were normal, and in vitro antigen responses with candida and tetanus toxoid were absent. Genetic testing with next generation whole gene sequencing revealed NFKB1 gene mutation with likely pathogenic variant, c.1300+1G>T.

Discussion/Conclusion: This case signifies the need for a low threshold of suspicion for an immune deficiency to yield to prompt work up, diagnosis, and best treatment for affected individuals.

Hereditary Angioedema Type 1 (HAE1) Affected Family and Their Response to Berotralstat

Steve M Dorman, Jr

Methods: A retrospective review was conducted between 2016 and 2022 of adult patients who were treated at our affiliated clinics, had HAE1, were of the same family, and received berotralstat. Charts were evaluated to document response to therapy and adverse drug reactions.

Results: Three patients were identified with HAE1 of the same family, two who received berotralstat. At age 16, the first patient began experiencing abdominal and extremity angioedema events. Age 30, she suffered laryngeal angioedema resulting in emergent intubation and was subsequently diagnosed with HAE1, starting danazol. Age 51, she transitioned to prophylactic plasma-derived nanofiltered C1 esterase inhibitor intravenously and later had increasing difficulty gaining intravenous access for this agent's delivery. Breakthrough angioedema episodes occurred, including perioperative laryngeal swelling. Age 53, she switched to lanadelumab-flyo subcutaneously, still having extremity swelling events. Age 56, she transitioned to berotralstat and over 11 months she had 1 hand swelling event and remained without adverse drug reaction. The second patient began having symptoms age 15, with angioedema events 3 times annually. Age 27, angioedema episode frequency increased to 3 times monthly. Age 32, she suffered acute tongue swelling, receiving ecallantide in a hospital emergency department. She was diagnosed HAE1, starting C1 esterase inhibitor subcutaneous prophylaxis and was on this agent 2 years with 1 foot angioedema event. Age 34 she began having extremity swelling 3 times monthly. Age 35, she switched to berotralstat, experiencing 2 weeks of mild, transient abdominal discomfort. She continued berotralstat 11 months without angioedema or medication adverse event.

Conclusion: Berotralstat was an effective medication for the management of active HAE1 in a familial cohort. Adverse effects associated with berotralstat were mild and transient. Larger prospective studies should be performed to confirm these observations.

Eosinophilic Esophagitis Patients Treated with Placebo in the Phase 2 Proof-of-Concept and Phase 3 TREET Studies: Esophageal Eosinophil Count Does Not Correlate With the Endoscopic Reference Score Remodeling Subscore

Ikuo Hirano, Marc E. Rothenberg, Jonathan M. Spergel, Seema Aceves, Matthew Greenhawt, Alain M. Schoepfer, Zhen Chen, Angela Khodzhayev, Yamo Deniz, Paul J. Rowe, Juby A. Jacob-Nara

Introduction: Although eosinophils are the hallmark of eosinophilic esophagitis (EoE) with threshold levels required for diagnosis, their exact role is unclear. EoE-Endoscopic Reference Score (EREFS) assesses endoscopic inflammatory (edema/exudates/furrows) and remodeling (rings/strictures) features. We assessed the relationship between peak esophageal intraepithelial eosinophil count (eos/high-power field [hpf]) and EREFS in placebo-treated EoE patients from two clinical trials: phase 2 proof-of-concept (POC; NCT02379052) and part A of the 3-part, phase 3 TREET (Phase3-PartA; NCT03633617).

Methods: POC was a 12-week trial in adults; Phase3-PartA was a 24-week trial in adults and adolescents. Endoscopic esophageal examination was performed at baseline and end of treatment (EOT) and scored for total score/inflammatory subscores/remodeling subscores using EREFS (higher scores=greater severity). Peak eos/hpf was measured from pinch biopsies of proximal/mid/distal esophagus at baseline/EOT. Pearson correlations were performed between eos/hpf and EREFS total, subscores, and components at baseline/EOT/change from baseline at EOT.

Results: A strong correlation (correlation coefficient [r]>0.5) was observed between total peak eos/hpf and EREFS total score in Phase3-PartA at baseline (r=0.5625; P=0.0001). Moderate-to-strong correlations (r>0.3) were observed between total peak eos/hpf and EREFS inflammation subscore and edema/exudates/furrows individual components in both studies (POC: inflammation subscore baseline r=0.3591 [P=0.0850], edema baseline r=0.3431 [P=0.1013], exudates baseline r=0.3075 [P=0.1453]; Phase3-PartA: inflammation subscore baseline r=0.5482 [P=0.0002], exudates baseline r=0.4735 [P=0.0020], furrows baseline r=0.3803 [P=0.0496]). Correlations between total peak eos/hpf with EREFS remodeling subscore and rings/stricture components were not significant (P=0.07 to 0.94).

Conclusions: In these EoE patients, moderate-to-strong correlations were observed between eos/hpf and endoscopic inflammation markers. No strong correlations were observed between total/proximal/mid/distal peak eos/hpf and endoscopic parameters of remodeling. These data support a role for intact eosinophils in esophageal inflammatory changes in EoE and demonstrate the need for both histologic and endoscopic evaluation. Further study, with larger sample sizes, is required to verify these findings in other contexts.

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Correlations of Distensibility Plateau and Endoscopic Reference Score in Adult Patients With Active Eosinophilic Esophagitis

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Introduction: Patients with eosinophilic esophagitis (EoE) with a fibrostenotic phenotype are at a higher risk for food impaction and have a higher burden of dysphagia. The Endoscopic Reference Score (EREFS) assesses esophageal features (edema, rings, exudates, furrows, strictures) and is one method to identify inflammation/fibrostenosis in patients with EoE. Distensibility evaluation of the esophagus using the functional luminal imaging probe (EndoFLIP) further characterizes esophageal function in patients with EoE. This post hoc analysis assesses the relationship between baseline esophageal distensibility and fibrostenotic/inflammatory phenotypes in adult patients with EoE from the phase 2 proof-of-concept (POC) study of dupilumab (NCT02379052).

Methods: 47 patients were enrolled and randomized to receive placebo or dupilumab. Endoscopy was performed at baseline, and severity was scored using EREFS (higher scores=greater severity). EREFS were summed for inflammatory (edema+exudates+furrows) and remodeling (rings+strictures) subscores. Esophageal distensibility plateau was measured by EndoFLIP. Multivariate linear regression model analyses compared esophageal distensibility plateau and EREFS total score, and inflammation and remodeling subscores in patients from both treatment arms at baseline. The estimated coefficients and P values were derived using a multivariate linear regression model, adjusting for age and prior dilations.

Results: 35 (74%) of patients were included in this analysis. Correlations were observed between esophageal distensibility plateau and the EREFS remodeling subscore (coefficient −0.95058; P=0.0344) and rings component score (coefficient −1.52272; P=0.0466) at baseline. However, esophageal distensibility plateau did not correlate with the total EREFS score (coefficient −0.47845; P=0.1399) or EREFS inflammation subscore (coefficient −0.00532; P=0.9921).

Conclusions: In the phase 2 POC study in adults with active EoE, esophageal distensibility at baseline was associated with the EREFS remodeling subscore. Esophageal distensibility was not associated with the EREFS inflammation subscore. This suggests a relationship between esophageal distensibility and endoscopic fibrostenotic phenotype. Further analyses with a larger dataset are required to validate this hypothesis.

F30

Dupilumab Reduces Biomarkers of Type 2 Inflammation in Adult and Adolescent Patients With Eosinophilic Esophagitis in Parts A and C of a Three-Part, Phase 3 LIBERTY EoE TREET Study

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Introduction: Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases, including EoE. Part A of the 3-part, phase 3 LIBERTY-EoE-TREET study (NCT03633617) demonstrated the efficacy and safety of weekly dupilumab 300mg vs placebo in adolescent and adult patients with EoE for 24 weeks. For patients completing Part A, Part C was a 28-week extended active treatment period to evaluate efficacy and safety of weekly dupilumab 300mg for 52 weeks. This analysis assessed dupilumab effect on biomarkers of type 2 inflammation in Part C.

Methods: Of 81 patients (42 dupilumab; 39 placebo) enrolled in Part A, 77 continued to dupilumab in Part C (40 dupilumab [dupilumab/dupilumab]; 37 placebo [placebo/dupilumab]). Median changes from Part A baseline (ΔBL) in serum thymus and activation-regulated chemokine (TARC), plasma eotaxin-3, and serum total IgE were assessed.

Results: Part A baseline biomarker levels were similar across treatment groups. In Part A, at Week 24, median ΔBL (Q1,Q3) for dupilumab vs placebo was: TARC −115.5pg/mL (−204.0,−60.0) vs −35.0pg/mL (−67.0,32.0); eotaxin-3 −88.6pg/mL (−212.0,−47.0) vs −9.0pg/mL (−148.0,53.0); and total IgE −45.7kU/L (−198.0,−23.7) vs −8.6kU/L (−72.0,4.7) (all nominal *P*<0.0001). In Part C, at Week 52, median ΔBL (Q1,Q3) for dupilumab/dupilumab and placebo/dupilumab was: TARC −98.0pg/mL (−182.0,−37.0) and −122.0pg/mL (−194.0,−28.0); eotaxin-3 −118.0pg/mL (−225.3,−63.8) and −160.9pg/mL (−367.0,−104.6); and total IgE −62.9kU/L (−410.0,−35.4) and −57.6kU/L (−178.8,−28.7). Overall safety was consistent with the known dupilumab safety profile in Part C; TEAEs occurring in ≥10% patients in dupilumab/dupilumab and placebo/dupilumab groups were injection-site reactions (10.0%/21.6%) and injection-site erythema (10.0%/13.5%).

Conclusions: Dupilumab suppressed TARC, eotaxin-3, and total IgE in EoE patients over 52 weeks, consistent with prior assessments in EoE and other type 2 inflammatory diseases. Placebo/dupilumab patients in Part C showed similar treatment effects to dupilumab patients in Part A.

F31

New Onset Angioedema (AE) in a 50-year-old Female Unveiling One Decade of Splenomegaly

Donya Imanirad MD, Farnaz Tabatabaian MD

Introduction: Acquired Angioedema (AAE) is a rare disease associated with several lymphoproliferative and autoimmune diseases. A new onset angioedema led to diagnosis of marginal zone lymphoma in a woman with longstanding history of splenomegaly.

Case: A 51-year-old female with history of post-partum ovarian vein thrombosis presents with one year history of recurrent angioedema of the face, hands, forearm, and the genital area. AE was not responsive to epinephrine and minimally responsive to systemic corticosteroid. Lab test results were significant for low C2, C4 and both low C1 inhibitor level and function. C1q was also diminished. Additionally, she had low hemoglobin and platelet counts. Atypical lymphocytes were seen on blood smear. Ultrasound of the abdomen showed enlarged spleen at 20.6 cm. Patient was prescribed icatibant (bradykinin receptor 2 inhibitor) for acute AAE with good response. History revealed presence of splenomegaly for ten years prior to presentation with AE. Peripheral flow cytometry showed monoclonal B-cell population (Kappa) consistent with low grade B-cell lymphoma. Bone marrow biopsy was consistent with stage IV splenic marginal zone lymphoma. Patient was started on rituximab with resolution of AE.

Discussion: The patient lived with splenomegaly and anemia that was not worked up completely until AE led to diagnosis of stage IV marginal zone lymphoma. Clonal B-cell proliferation is often the pathology underlying AAE leading to production of C1-INH-neutralizing autoantibodies and to non-Hodgkin's-lymphoma (NHL). About 62.5% of patients with AAE and C1-INH-deficiency have or will develop NHL. Thus, patients with angioedema and acquired c1-inhibitor deficiency should undergo malignancy evaluation.

F32

Lymphoma in Partial DiGeorge Syndrome

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Introduction: The increased risk of malignancy in of partial DiGeorge syndrome (pDGS) is likely due to tumor suppressor gene deletions and immune dysregulation secondary to immune defects involving CD3+, CD4+, and CD8+ T-cell lymphopenia. There is a paucity of data regarding the association of pDGS and lymphoma. Herein we describe two patients with pDGS and autoimmunity requiring immunosuppression who developed Epstein-Barr virus (EBV)-induced lymphomas: diffuse large B-cell lymphoma (DLBCL) in a child and mixed cellularity (MC) classical Hodgkin lymphoma (cHL) in a young adult.

Case presentations:
Patient 1 with tetralogy of Fallot (TOF) was diagnosed with pDGS at birth. At 6 years old she developed autoimmune hepatitis, severe neutropenia, and severe immune thrombocytopenia (ITP) requiring high-dose glucocorticosteroid therapy. Immune profile revealed elevated IgM, low CD8+ T-cells, a high proportion of CD45RO+ memory T-cells, and low CD45RA+ naïve T-cells. Attempts to wean glucocorticosteroids were unsuccessful and required addition of azathioprine and cyclosporine. At 11 years old she was diagnosed with stage III EBV-positive DLBCL.

Patient 2 with TOF was diagnosed with pDGS at birth. At 8 years old he developed ITP requiring pulse-dose glucocorticosteroid therapy, immunomodulating doses of intravenous immunoglobulin, and rituximab. Immune profile during his teenage years revealed hypogammaglobulinemia, elevated IgM, low CD3+ and CD4+ T-cells, and undetectable B-cells. At 26 years old he was diagnosed with stage IIIB non-bulky, EBV-positive MC cHL.

Discussion: Defective immune surveillance and impaired T-cell function in primary immunodeficiency diseases result in an inability to eradicate virally infected cells and cells with abnormal proliferation. In these instances, both patients underwent prolonged periods of immune suppression for treatment of ITP preceding the onset of lymphoma, potentially contributing to the increased risk of lymphoma.

Conclusions: The incidence and spectrum of lymphoma subtypes in pDGS is unknown. There is a lack of epidemiologic, clinical, treatment, and outcome data in this population and remains an area of unmet need.

Eastern Allergy Conference
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Scientific Posters S1-S32 will be on display in the Ponce Foyer during the coffee break, 10:15 – 11:00am, Saturday June 4, 2022

Not for CME Credit

S1

EValuating trEatment RESponses of dupilumab versus omalizumab in Type 2 patients: The EVEREST Trial

De Prado Gomez L, Khan A H, Peters AT, Bachert C, Wagenmann M, Heffler E, Hopkins C, Hellings P, Zhang M, Xing J, Rowe P, Jacob-Nara J

Rationale: Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) and asthma are chronic type 2 inflammatory diseases. Dupilumab (DUP), a fully human monoclonal antibody, blocks the shared receptor component for interleukin-4/-13, key and central drivers of type 2 inflammation. Omalizumab (OMZ) is a humanized, monoclonal antibody which blocks the action of IgE. Both DUP and OMZ are approved for the treatment of uncontrolled CRSwNP or nasal polyps and asthma. To contribute to evidence-based decision making for treating respiratory diseases, head-to-head studies are required to investigate the comparative efficacy and safety of these interventions.

Methods: EVEREST (NCT04998604) is a global, multicenter, randomized (1:1), double-blind, active-controlled study to compare the efficacy and safety of DUP versus OMZ over 24 weeks of treatment as add-on to nasal corticosteroid therapy. Approximately 422 adult patients with CRSwNP, with ongoing symptoms of nasal congestion and loss of smell, and coexisting asthma will be recruited across 15 countries.

Result: The primary objective is to assess the comparative efficacy of DUP vs OMZ in reducing NP size and improving sense of smell (change from baseline to week 24 in NP score and University of Pennsylvania Smell Identification Test, respectively). Secondary objectives include the assessment of lung function (pre-BD FEV_1), nasal peak inspiratory flow, nasal congestion, quality of life (SNOT-22), asthma control, and safety.

Conclusions: EVEREST is the first head-to-head trial assessing the comparative efficacy and safety of two biologics in patients with severe CRSwNP and comorbid asthma. EVEREST will provide direct comparative evidence to guide physicians when selecting optimal therapy for their patients.

S2

Continued Safety of Peanut (*Arachis hypogaea*) Allergen Powder-dnfp in Children and Teenagers With Peanut Allergy: Pooled Analysis From Controlled and Open-Label Phase 3 Trials

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Introduction: Peanut (*Arachis hypogaea*) allergen powder-dnfp (PTAH; previously 'AR101') is a once-daily oral immunotherapy approved by the FDA (Palforzia®) to mitigate allergic reactions that may occur with accidental peanut exposure in peanut-allergic individuals aged 4-17 years. Previously, safety data from trial participants receiving PTAH over ≤3.5 years were pooled/described; analyses including an additional year of data (totaling ≤4.5 years) are presented here.

Methods: Safety data from six PTAH clinical trials (n=3, controlled; n=3, open-label extension) were pooled and assessed (cut-off July 31, 2021).

Results: Of 1127 individuals receiving ≥1 PTAH dose, representing 2323 exposure-years, most participants experienced ≥1 treatment-related adverse event (TRAE; n=1021; 90.6%). Median duration of PTAH exposure was 21.0 (IQR 10.3-41.3) months. Maximum AE severity was predominantly mild (n=395; 35.0%) or moderate (n=662; 58.7%); 62 (5.5%) participants reported severe or life-threatening AEs. Serious AEs (SAEs) occurred in 44 (3.9%) participants; seven (0.6%) experienced treatment-related SAEs. Overall, 149 (13.2%) participants discontinued due to AEs. Exposure-adjusted AE and TRAE rates were 73.6 and 56.4 events/exposure-years, respectively, during updosing and decreased to 13.6 and 7.6 events/exposure-years during 300-mg maintenance. Exposure-adjusted rates of systemic allergic reactions of any severity and of epinephrine use were low during Year 1 (0.26; 0.19) and decreased in Years 2 (0.16; 0.11), 3 (0.07; 0.07), and 4 (0.07; 0.05) of maintenance.

Conclusions: PTAH safety data, characterized over up to 4.5 years, consistently show AEs trend downward during continued maintenance dosing. Furthermore, systemic allergic reactions and epinephrine use occur less frequently, also trending downwards as treatment continues.

S3

Manufacturing and Standardization of Peanut (*Arachis hypogaea*) Allergen Powder-dnfp for Use as an Oral Immunotherapy: Peanut Flour Source Material Lot Testing

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Introduction: Peanut allergy is typically lifelong, can lead to life-threatening reactions, and has few effective treatments. Lack of standardization of food products, including clinician-generated peanut preparations used for allergen immunotherapy, represents a barrier to optimizing safety/effectiveness of immunotherapy. Drug identity, quality, and purity are critical factors contributing to safety, effectiveness, and acceptability. Lack of drug standardization can lead to inefficacy from lack of purity or low potency, as reported for skin prick test extracts, as well as toxicity from inconsistent potency and contaminants. Peanut (*Arachis hypogaea*) allergen powder-dnfp (PTAH; Palforzia) is an oral immunotherapy approved by the US FDA and EU EC to mitigate allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in individuals aged 4-17 years. We summarize evaluation of the bulk peanut flour source material (partially defatted [12% fat], lightly roasted peanut flour from Golden Peanut and Tree Nuts company).

Methods: Immunodominant allergens' relative potency compared with an internally qualified reference standard was assessed using a validated ELISA test; aflatoxins were quantified using UPLC. Other quality attributes were also evaluated. Proportion of screened lots rejected as unsuitable for drug substance testing from 2018 to 2021 was reported.

Results: The proportion of screened lots rejected was 57% (n/N=8/14) in 2018, 38% (n/N=3/8) in 2019, 57% (n/N=4/7) in 2020, and 60% (n/N=3/5) in 2021. Furthermore, rejected lots differed from the standard by several fold. Reasons for rejection were quality (potency acceptance criteria for selection not met for ≥1 component allergen) or safety (aflatoxin level near the acceptability threshold).

Conclusions: Most single-source peanut flour material failed to meet prespecified criteria for drug substance testing and PTAH product development. Ensuring standardization across lots, in addition to thorough confirmation of drug identity, quality, and purity through all phases of product development, is critical to optimizing overall immunotherapy safety/efficacy.

S4

Efficacy and Safety of the Anti-Fel d 1 Antibodies REGN1908/1909 in Cat-Allergic Patients with Allergic Rhinitis During Natural Cat Exposure in the Home: Design of a Phase 3, Randomized, Placebo-Controlled Study

Deepti Deshpande, Michelle DeVeaux, Robert Dingman, Jennifer Maloney, Peter Creticos

Introduction: Cat allergens are an important indoor allergen and a common cause of allergic rhinoconjunctivitis and/or asthma. The immunodominant allergen in cat dander is Felis domesticus allergen 1 (Fel d 1), a secretoglobulin; up to 95% of cat allergic individuals are sensitized to Fel d 1. REGN1908/1909, two monoclonal antibodies (mAbs) that bind independently and non-competitively to Fel d 1, are being developed as a passive immunotherapy for the treatment of cat allergy. REGN1908/1909 was previously demonstrated to reduce nasal symptoms upon exposure to cat allergen during a nasal allergen challenge and to prevent cat allergen induced decline in FEV1 in cat allergic mild asthmatics upon controlled exposure in an environmental exposure unit. Here, we describe the design of a trial (NCT04981717) with the objective of assessing the efficacy and safety of REGN1908/1909 to reduce symptoms of allergic rhinitis (AR)/conjunctivitis and allergy rescue medication use during natural cat exposure compared with placebo.

Methods: This phase 3, randomized, double-blind, placebo-controlled study will enroll approximately 630 cat-allergic adult and adolescent (≥12 years of age) patients with AR, with or without conjunctivitis and/or asthma, who are substantially symptomatic despite using standard of care allergy medications while living with a cat. The study will include a screening period of up to 12 weeks, a treatment period of 60 weeks, and a safety follow-up period of 12 weeks. Patients will be randomized 1:1 to subcutaneous REGN1908/1909 600 mg or placebo administered every 12 weeks (Q12W). The primary endpoint is the combined symptom and medication score, a composite of the daily nasal/ocular symptoms and allergy medication use, averaged over the last 12 weeks of the treatment period, in patients who receive REGN1908/1909 versus placebo.

Conclusions: This is the first large phase 3 trial evaluating a novel passive immunotherapy, REGN1908/1909, in cat allergic patients living with cats.

US Expert Consensus On Short-acting Beta Agonist (SABA) Reliever Medication Use For Asthma Clinical Decision-making: A Mixed-method Delphi Adjudication Approach

Greg Bensch, Rajan Merchant, Maeve O'Connor, Mario Castro

Introduction: Increased use of SABA reliever medication has been recognized as a problem for >30 years and many guidelines lack specific overuse recommendations. Thus, updated expert-led review/consensus is needed to provide guidance on clinical action to take in response to reliever usage patterns.

Methods: In 2021, a rigorous iterative mixed-methods consensus-building process was undertaken: 1) online physician survey; 2) forum discussion with evidence review and SABA statement development; 3) Delphi adjudication videoconference/polling. Experts rated levels of agreement with statements on a 5-point Likert scale; median score and interquartile range were calculated. Consensus to accept was defined as lower quartile ≥4 ("agree").

Results: 100 primary/specialty physicians completed the survey. Subsequent expert panel consensus (median Likert score, IQR), as reliever use of ≥3 SABA canisters/year is associated with increased risk of exacerbation/asthma-related death, refill rates should be monitored closely (5, 4.75-5) and SABA use history should be solicited at every patient encounter (5, 4.75-5). Individual SABA use data, rather than absolute thresholds, should typically guide clinical actions in response to SABA use (5, 4.5-5). SABA use episodes ≥50% and ≥100% above the patient's baseline (4, 4-4; 5, 4.75-5, respectively) are considered likely to indicate impending/ongoing exacerbation, as does reliever use exceeding ≥5 episodes/week (4.5, 4-5). Reliability of usage frequency information provided during patient assessment should be considered (4.5, 4-5); experts agreed that patient-sourced information is likely inaccurate (5, 5-5) and that pharmacy refill data may not correlate with actual use (4, 4-4.25); therefore, use of digital health tools to assess reliever medication use should be considered (4, 4-5).

Conclusions: Experts recommended consideration of thresholds/patterns for clinical action and basing action on individualized understanding of patients' asthma clinical profiles. Improving validity/reliability of reliever usage data offers potential to aid asthma management. Future asthma guidelines should include specific recommendations regarding this topic.

Application Of Modified Delphi Expert Consensus Thresholds On SABA Reliever Use In Asthma To Data Obtained From A 12-week Study Of A Digital Inhaler In Suboptimally Controlled Asthma Patients

John Oppenheimer, Maureen George, Jay Portnoy, Randall Brown

Introduction: US asthma experts developed clinical statements regarding excessive SABA reliever use via a rigorous consensus-building process, and agreed that clinical decision-making should optimally be based upon individualized insights into patients' reliever use profiles, with thresholds for clinical action informed by baseline and weekly usage data. These data obtained from the albuterol Digihaler (90μg/dose) can provide an objective platform for assessment of proposed clinical thresholds.

Methods: Previously, patients with ≥1 asthma exacerbation/prior year and suboptimal asthma control (ACQ ≥1.5) used albuterol Digihaler for 12 weeks in an open-label study (NCT02969408). In this analysis, clinical decision threshold rules derived from statements agreed upon during the modified Delphi process were applied to data downloaded from the devices.

Results: Of 359 patients who made ≥1 valid (i.e. peak inspiratory flow ≤120L/min with no errors in use) inhalation and completed the study, 64 (18%) had a clinically confirmed in-study asthma exacerbation.104/359 (29%) exhibited a rate of SABA reliever use during the 12-week study, equivalent to ≥3 canisters/year, associated with increased risk of exacerbation and asthma-related death, including 33/64 (52%) of those who had exacerbation(s) during the study and 71/295 (24%) of those who did not. 319/359 (89%) of patients met a consensus decision threshold of usage ≥100% over their personal baseline during ≥1 study week(s); 260/359 (72%) met a very conservative threshold of usage ≥200% above their baseline. 62/359 (17%) made ≥25 valid inhalations in a week - a level of reliever usage associated with unanimous consensus of likely impending/ongoing exacerbation - including 40/295 (14%) patients without confirmed exacerbation(s).

Conclusions: These findings suggest that elevated SABA reliever use among suboptimally controlled asthma patients may be far more commonplace than previously understood. The advent of digital inhalers offers new potential to address this challenge and develop individualized preventive approaches informed by reliable reliever usage data.

Efficacy of Dupilumab in Quadrants of Elevated- vs Low- Type 2 Biomarkers in Children With Uncontrolled, Moderate-to-Severe Asthma: LIBERTY ASTHMA VOYAGE

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Introduction: Dupilumab, a human mAb, blocks the shared receptor component for IL-4/13, key and central drivers of type 2 inflammation. In VOYAGE (NCT02948959), dupilumab 100/200mg vs placebo every 2 weeks for 52 weeks reduced severe asthma annualized exacerbation rate (AER) and improved percent predicted pre-bronchodilator FEV1 (ppFEV1) in children aged 6-11 years with uncontrolled, moderate-to-severe asthma. We evaluated the predictive value of baseline blood eosinophil and FeNO levels as biomarkers for dupilumab response.

Methods: The population was clustered into quadrants based on baseline blood eosinophil (< vs ≥150cells/μL) and FeNO levels (< vs ≥20ppb). The relative risk (RR) for AER and change from baseline in ppFEV1 at Week 12 were evaluated.

Results: AER was reduced in the high eosinophils/low FeNO (N=137, RR: 0.473; 95%CI: 0.262–0.851) and high eosinophils/high FeNO (N=184, RR: 0.351; 95%CI: 0.204–0.605) quadrants, and was numerically lower in the high FeNO/Low eosinophils (N=19, RR: 0.449; 95%CI: 0.051–3.989) quadrant, but not in the low eosinophils/low FeNO (N=56, RR: 1.295; 95%CI: 0.357–4.690) quadrant. Values for ppFEV1 were numerically higher in dupilumab- vs placebo-treated patients at Week 12 in all quadrants: high eosinophils/low FeNO (LS mean difference [LSMD]: 2.90; 95%CI: -1.51–7.31), high eosinophils/high FeNO (LSMD: 6.44; 95%CI: 2.01–10.87), high FeNO/low eosinophils (LSMD: 3.61; 95%CI: -22.71–29.92), low eosinophils/low FeNO (LSMD: 1.38; 95%CI: -6.13–8.90).

Conclusions: Dupilumab reduced exacerbations and led to numeric improvements in lung function among children with either elevated blood eosinophils and/or FeNO.

Dupilumab Improves Quality of Life in Caregivers of Children With Uncontrolled Moderate-toSevere Asthma: LIBERTY ASTHMA VOYAGE Study

Alessandro G. Fiocchi, Wanda Phipatanakul, Sandy Durrani, Jeremy Cole, Dongfang Liu, Jérôme Msihid, David J. Lederer, Megan Hardin, Yi Zhang, Asif H. Khan

Introduction: VOYAGE (NCT02948959) demonstrated efficacy/safety of dupilumab in children aged 6–11 years with uncontrolled moderate-to-severe asthma. We assessed QoL improvement in caregivers of pediatric patients in VOYAGE.

Methods: Eligible children were randomized to add-on dupilumab or matched placebo by bodyweight. Caregivers of patients aged 7–11 years completed the Pediatric Asthma Caregiver QoLQuestionnaire (PACQLQ), at study baseline and up to Week (Wk) 52. PACQLQ global scores (range 1–7; higher scores=better QoL) of caregivers of patients with type 2 asthma phenotypes (baseline blood eosinophils ≥150 cells/μL or FeNO ≥20 ppb; n=318) and patients with baseline eosinophils ≥300 cells/μL (n=239) were analyzed.

Results: At baseline, 25% of caregivers reported their work was impacted 'a lot' by the children's asthma, and 33% reported 'very worried or concerned' about their child leading a normal life, reflecting high burden on caregiver's QoL. For caregivers of dupilumab patients, global PACQLQ scores improved by Wk36 in the type 2 population (LS mean [95% CI] difference in change from baseline vs placebo: 0.40 [0.16−0.64; P=0.0013]) and by Wk12 in the population with eosinophils ≥300 cells/μL (LS mean [95% CI] difference vs placebo: 0.34 [0.01−0.67; P=0.0445]. Activity limitation domain scores improved by Wk24 in the type 2 population (LS mean [95% CI] difference vs placebo: 0.35 [0.10−0.60; P=0.0072]) and in the population with eosinophils ≥300 cells/μL (LS mean [95% CI]difference vs placebo: 0.40 [0.10−0.71; P=0.0100]). Emotional function domain scores significantlyimproved by Wk36 in the type 2 population (LS mean [95% CI] difference vs placebo: 0.41 2 [0.16−0.67; P=0.0017]) and by Wk12 in the population with eosinophils ≥300 cells/μL (LS mean [95% CI] difference vs placebo: 0.39 [0.04−0.73; P=0.0292]).

Conclusion: Dupilumab treatment in patients aged 7–11 years with uncontrolled asthma improvedcaregiver QoL, demonstrated by PACQLQ scores and activity limitation and emotional function domain scores.

Persistent Reductions in OCS Use in Patients With Severe, OCS-Dependent Asthma Treated With Dupilumab: LIBERTY ASTHMA TRAVERSE Study

Mark Gurnell, Christian Domingo, Klaus F. Rabe, Andrew Menzies-Gow, David Price, Guy Brusselle, Michael E. Wechsler, Changming Xia, Michel Djandji, Rebecca Gall, Juby A. Jacob Nara, Paul J. Rowe, Yamo Deniz, Shahid Siddiqui

Introduction: LIBERTY ASTHMA TRAVERSE (NCT02134028 evaluated the long-term safety, tolerability, and efficacy of add-on dupilumab in patients rolled over from previous dupilumab studies, including VENTURE. In this study, we assessed dupilumab efficacy in patients with OCSdependent severe asthma and varying baseline levels of disease burden as measured by their OCS starting dose.

Methods: Patients with OCS-dependent asthma received add-on dupilumab 300mg q2w or placebo for 24 weeks during VENTURE (parent study), followed by add-on dupilumab 300mg q2w for up to 96 weeks in TRAVERSE (dupilumab/dupilumab and placebo/dupilumab groups, respectively). Patients were stratified based on their baseline OCS dose during VENTURE (≤10 or >10 mg/day). OCS dose percentage reduction from parent study baseline at TRAVERSE Weeks 0 and 48, annualized rate of severe asthma exacerbations (AER) during VENTURE and TRAVERSE, and pre-bronchodilator FEV1at TRAVERSE Weeks 0 and 48 were assessed.

Results: 187 patients (≤10 mg/day, placebo/dupilumab: n=61; dupilumab/dupilumab: n=60; >10 mg/day, placebo/dupilumab: n=36; dupilumab/dupilumab: n=30) were included in these analyses. The greater reductions in daily OCS use observed in patients on dupilumab at VENTURE study end continued during TRAVERSE in dupilumab/dupilumab patients (≤10 mg/day: −82.8%, >10 mg/day: −74.7% at TRAVERSE Week 48). In patients who were on placebo during VENTURE and were switched to dupilumab in TRAVERSE (placebo/dupilumab), OCS use was further reduced, irrespective of OCS use at baseline (≤10 mg/day: −49.6%, >10 mg/day: −66.5% at TRAVERSE Week 48). Despite these continued reductions in OCS use, AER continued to decline during TRAVERSE (range: 0.284–0.599) and pre-bronchodilator FEV1 greatly improved (range at TRAVERSE Week 48: 1.83–1.92L).

Conclusions: Dupilumab reduced OCS dose and improved and maintained clinical efficacy outcomes of asthma, regardless of baseline OCS starting dose. As observed during VENTURE, dupilumab demonstrated persistently high reduction in OCS use without a tapering schema of reduction in TRAVERSE.

Dupilumab Shows Long-Term Improvements in Lung Function Parameters in Patients With Asthma With and Without Comorbid Chronic Rhinosinusitis and/or Nasal Polyposis

Andrew Menzies-Gow, Patrick Berger, Anju T. Peters, Piotr Kuna, Klaus F Rabe, Arman Altincatal, Michel Djandji, Shahid Siddiqui, Yamo Deniz, Juby A. Jacob-Nara, Paul J. Rowe

Introduction: This post hoc analysis of TRAVERSE (NCT02134028) assessed the long-term effect of dupilumab on lung function parameters in patients from QUEST (NCT02414854) with moderate-to-severe asthma with and without comorbid chronic rhinosinusitis and/or nasal polyposis (CRS/NP).

Methods: Patients with uncontrolled, moderate-to-severe asthma received add-on dupilumab 200or 300 mg every 2 weeks (q2w) or matched placebo for 52 weeks during the QUEST parent study followed by add-on dupilumab 300 mg q2w for up to 96 weeks in TRAVERSE (dupilumab/dupilumab and placebo/dupilumab groups, respectively). Study duration shortened to 48 weeks following a protocol amendment; not all patients received 96 weeks of treatment. Changes from the parent study baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), forced expiratory flow at 25–75% of pulmonary volume (FEF25–75%), and FEV1/FVCratio at Weeks 0, 48, and 96 of TRAVERSE were evaluated in patients with and without self-reported comorbid CRS/NP.

Results: 111/517 (21.4%) placebo/dupilumab and 206/1,013 (20.3%) dupilumab/dupilumab patients had comorbid CRS/NP. Improvements in FEV1, FVC, and FEF25–75% observed during QUEST in dupilumab/dupilumab patients were sustained in patients with and without CRS/NP at Week 0 (n=205 and n=805) and through Week 96 (n=98 and n=349) in TRAVERSE. Placebo/dupilumab patients with and without comorbid CRS/NP (n=111 and n=405) showed rapid improvements in lung function parameters in TRAVERSE, with values sustained through Week 96 (n=55 and n=164). Minimal changes were seen in the FEV1/FVC ratio in dupilumab/dupilumab or placebo/dupilumab patients with and without CRS/NP.

Conclusions: Dupilumab demonstrated sustained, long-term improvements in lung function parameters in patients with moderate-to-severe asthma with and without comorbid CRS/NP. Patients who received placebo during QUEST showed a rapid improvement in lung function after initiating dupilumab in TRAVERSE, demonstrating a rapid and sustained lung function response to dupilumab, irrespective of the presence of comorbid CRS/NP.

Effectiveness of Benralizumab in Asthma Patients with Comorbid Nasal Polyps: Results from the ZEPHYR 2 Study

Donna Carstens, Eduardo Genofre, Benjamin Emmanuel, Fan Mu, Joshua A. Young

INTRODUCTION: Benralizumab reduces asthma exacerbations in patients with severe eosinophilic asthma, among whom nasal polyps is a common comorbidity. However, the real-world outcomes of benralizumab in this comorbid population, specifically by prior nasal polyps surgery status, has not yet been characterized.

METHODS: Asthma patients with comorbid nasal polyps who initiated benralizumab (index date) were selected from a large US insurance claims source (November 2016–June 2020). Patients who met the following criteria were included: ≥2 records of benralizumab, ≥2 asthma exacerbations, diagnosed with nasal polyps, and aged ≥12 years. Asthma exacerbation rates and nasal polyps-related oral corticosteroid (OCS) use were compared during the 12-month pre-index and 12-month post-index periods, stratified by pre-index nasal polyps surgery status.

RESULTS: Of 241 patients identified, 66 had pre-index nasal polyps surgery (surgery cohort) and 175 did not (non-surgery cohort). Among all patients (mean age 47-51 years; female 55-56%), common comorbidities were allergic rhinitis (79-84%) and gastroesophageal reflux disease (32-38%). The surgery cohort experienced a 57% reduction in asthma exacerbations comparing the pre- vs. post-index periods, and the non-surgery cohort saw a 59% reduction (both p<0.001). By inpatient, emergency, and outpatient setting, the surgery cohort experienced 61%, 55% and 57% reductions and the non-surgery cohort had 49%, 41%, and 63% reductions, respectively (all p<0.05). In addition, the percentage of patients with nasal polyps-related OCS decreased (surgery cohort: 77% pre- vs. 36% post-index; non-surgery cohort: 78% vs. 37%; both p<0.001). This corresponded to a decrease in nasal polyps-related cumulative OCS dosage from a median of 50mg to 0mg in the surgery cohort, and from 38mg to 0mg in the non-surgery cohort (both p<0.001).

CONCLUSIONS: Irrespective of prior nasal polyps surgery status, asthma patients with comorbid nasal polyps experienced a significant reduction in asthma exacerbation rates and OCS use after initiating benralizumab treatment.

Towards Clinical Remission in Severe Asthma: An Analysis of Patients Treated with Benralizumab in the Phase 3b ANDHI Trial

Tim W. Harrison, Renaud Louis, Donna Carstens, David Cohen, Rohit Katial

Rationale: A consensus definition for clinical remission (CR) in severe asthma (SA) was recently published. The ANDHI trial assessed the efficacy of benralizumab, an afucosylated monoclonal antibody directed against the interleukin-5 receptor α. This analysis applied a composite remission definition to characterize patient responses after 6 months of treatment with benralizumab.

Methods: ANDHI was a phase 3b randomized, double-blind, multicenter trial in patients with uncontrolled, severe eosinophilic asthma, and an Asthma Control Questionnaire 6 (ACQ-6) score ≥1.5. For this analysis, patients receiving long-term OCS at the baseline visit were excluded. Components of CR for this study were: zero exacerbations; zero OCS; ACQ-6 <1.5 or ≤0.75; and pre-bronchodilator forced expiratory volume in 1 sec (FEV1) increase ≥100mL. CR was defined as achieving all 4 components with an ACQ-6 ≤0.75 after 6 months of treatment. In ANDHI, 6 months was defined as Week 24 or the last recorded datapoint, which could have occurred after the Week 24 visit (labelled as Week 24); for patients with missing values for FEV1 or ACQ-6, available measurements within ±4 weeks of the labelled Week 24 were used.

Results: Overall, 331 patients receiving benralizumab were included in this analysis; 71.3% had zero exacerbations, 93.7% had zero OCS, 48.9% and 26.9% had ACQ-6 scores <1.5 and ≤0.75, respectively, and 56.2% had pre-bronchodilator FEV1 increases ≥100mL. In total, 81.3% of patients achieved ≥2 components and 51.7% achieved ≥3 remission components after 6 months. After 6 months of treatment with benralizumab, 16.6% achieved CR, whereas 28.7% achieved all 4 remission components when the less stringent ACQ-6 threshold of <1.5 was used.

Conclusions: This analysis, using a novel definition of remission, suggests that CR may be achieved in SA through precision medicines that treat to target the underlying drivers of inflammation; further analyses out to 12-18 months are currently underway.

Benralizumab is Effective in Reducing Asthma Exacerbations: Results From The ZEPHYR 2 Study

Diego J. Maselli, Donna Carstens, Danni Yang, Fan Mu, Joshua Young, Erin E. Cook, Keith A. Betts, Yen Chung

EDUCATIONAL OBJECTIVE: Upon completion of this session, participants should be able to discuss the reduction in asthma exacerbations associated with the initiation of benralizumab among multiple cohorts of patients, including patients with varying blood eosinophil levels and prior biologic use.

INTRODUCTION: Previously, benralizumab demonstrated significant reductions in asthma exacerbations in multiple clinical trials and observational studies. To build on these findings, this study characterized the effectiveness of benralizumab on asthma exacerbations in a real-world setting.

METHODS: This was a retrospective cohort study using data from a large US insurance claims database (November 2016–June 2020). Asthma exacerbation reduction was evaluated in multiple cohorts: (1) patients with blood eosinophil measures available pre-benralizumab initiation (index), stratified at 150 cells/µL and 300 cells/µL thresholds; and (2) in patients who switched from omalizumab or mepolizumab to benralizumab. All patients were aged ≥12 years, with ≥2 records of benralizumab and ≥2 asthma exacerbations pre-index. Asthma exacerbation rates were described and compared 1 year pre- and post-index.

RESULTS: The eosinophil analysis included 429 patients (114 patients with <150 cells/µL, 315 patients with ≥150 cells/µL, 194 patients with <300 cells/µL, and 235 patients with ≥300 cells/µL). The switch analysis included 205 patients who used omalizumab pre-index and 144 patients who used mepolizumab pre-index. Across all cohorts, the mean age range was 50.1-54.7 years, and most patients were female (64.7%-76.3%). All groups experienced a significant reduction in asthma exacerbations post-index vs. pre-index (eosinophil <150 cells/µl: 52% reduction; eosinophil ≥150 cells/µl: 64%; eosinophil <300 cells/µl: 56%; eosinophil ≥300 cells/µl: 64%; omalizumab pre-index: 62%; mepolizumab pre-index: 53%; all p<0.001)

CONCLUSION: Significant reductions in asthma exacerbations were observed with benralizumab use in patients with varying blood eosinophil levels and patients who switched from omalizumab or mepolizumab.

Long-term effectiveness and safety of lanadelumab in the US and Canada: Findings from the EMPOWER Study

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Introduction: Efficacy and safety of lanadelumab in patients with HAE were demonstrated in the HELP (NCT02586805) and HELP OLE (NCT02741596) studies. Interim findings from the prospective, observational EMPOWER study are presented.

Methods: Patients were recruited from the US and Canada. Key inclusion criteria: HAE-C1-INH and ability to use mobile device for data collection. Patient visits occurred every 6(±2) months until month 36. In the current analysis, patients were "new lanadelumab users" (received <4 doses at time of enrollment) or "established lanadelumab users." Primary outcome in new users: HAE attack incidence rate ratios <69 days after initiation and after ≥70 days, versus pre-treatment; each individual serves as their own control.

Results: 93 patients were enrolled (15 new, 78 established users). Mean(SD) duration of drug exposure in the study for this interim analysis was 470.8(191.6) days. Overall, 17.2% reported prior LTP use with C1-INH, and 81.7% experienced comorbidities. Among new users, 53.3% experienced <1attacks/month prior to enrollment and mean(SD) HAE attack rate was 1.2(1.4) attacks/month before and 0.2(0.21) attacks/month after treatment [83.3% reduction]). Among established users, mean(SD) attack rate was 0.2(0.50) attack/month during 490.9(183.6) days of follow-up on average. Only 7.8% of established users discontinued lanadelumab (none due to adverse events [AEs]). Treatment-emergent AEs were reported by 24.5% of patients, most commonly infections (23.6%); 2% of patients reported serious AEs. No AEs were considered related to lanadelumab.

Conclusions: Real-world interim findings showed marked attack rate reductions, and no new safety signals were found. Lanadelumab demonstrated sustained control of attacks among established users; final results pending.

Impact of chronic spontaneous urticaria on health-related quality of life in the United States

Freedle K., Patil D., Balp M., McKenna S.J., Gupta S., Balkaran B. L.

Introduction: The objective of this analysis was to evaluate the burden of illness among patients diagnosed with chronic spontaneous urticaria (CSU) in the United States of America (USA).

Methods: Data from adult respondents with a self-reported physician diagnosis of CSU were collected from the 2019 USA National Health and Wellness Survey, a nationally representative sample. The burden of illness was analyzed using the SF-36v2 (Mental [MCS] and Physical Component [PCS] Summary scores), health utility scores (SF-6D, EQ-5D), Dermatology Life Quality Index (DLQI), Work Productivity and Activity Impairment (WPAI), Patient Health Questionnaire-9 (PHQ-9), General Anxiety Disorder-7 (GAD-7) and Urticaria Control Test (UCT).

Results: Among 635 patients with CSU, 53.2% were treated (prescription and/or OTC), 77.0% were poorly controlled [UCT score <12]. The mean (SD) DLQI score was 13.8 (11.2), and 54.2% reported DLQI>10. CSU impacted patient's mental health status (MCS score: 36.3 [10.5]) more than physical health status (PCS score: 40.1 [10.0]). SF-6D utility score was 0.54 [0.14] and EQ-5D was 0.62 [0.33]. The mean (SD) GAD-7 score was 10.5 (7.2) with 21.1% reporting moderate (10-14) anxiety and 33.7% reporting severe (15-21) anxiety. The mean (SD) PHQ-9 score was 13.5(8.9), with 14.9% reporting moderately severe (15-19) depression and 31.8% severe (20-27) depression. Mean [SD] percentage absenteeism (36.5% [26.1]), presenteeism (67.2% [34.9]) and overall work productivity impairment (73.1% [34.2]) was reported among the employed patients. Mean [SD] percentage activity impairment among all CSU patients was 62.6% [34.1].

Conclusion: The majority of CSU patients had poor disease control and showed a high impact on mental health and impairment of work and activities.

Prevalence and clinical profile of patients with chronic spontaneous urticaria in the USA

Patil D., Freedle K., Balp M., McKenna S.J., Gupta S., Balkaran B. L.

Introduction: The objective of this analysis was to estimate the prevalence and describe the clinical profile and healthcare resource utilization (HCRU) amongst adult patients with chronic spontaneous urticaria (CSU) in the United States of America (USA).

Methods: Data from adult respondents with a self-reported physician diagnosis of CSU was collected from the 2019 National Health and Wellness Survey (NHWS), a nationally representative sample of the USA population. Patients' demographics, clinical characteristics and HCRU in the last 6 months were collected and analyzed using descriptive statistics. Weighted-prevalence of CSU was calculated using the 2018 national census projections (adjusted for age, sex, race, and education).

Results: Among 74,994 respondents, 635 CSU diagnosed, 51.7% female, 76.0% Caucasian. Mean [SD] age at diagnosis (37.0 [17.1]) and at data collection (39.5 [12.6]) years. Charlson Comorbidity Index score of 1 and 2+ was reported in 9.3% and 39.2%, respectively. Self-reported physician diagnosed comorbidities included: allergies (30.9%), depression (20.0%), anxiety (17.6%), asthma (12.4%), sleep difficulties (8.2%), atopic dermatitis (6.0%) and psoriasis (4.3%). Diagnosis was mostly confirmed by allergist (39.8%) or primary care physician (GP) (36.3%). Total HCRU included (%; mean (SD) visits): all healthcare professionals (96.5%; 8.25 [11.82]), ER visits (60.2%; 2.24 [4.28]) and hospitalizations (55.9%; 2.46 [7.66]). The most frequent specialty visits were GP (48.7%; 2.18 [2.34]), allergist (29.6%; 2.80 [4.27]), dermatologist (19.2%; 1.93 [1.53]). The estimated weighted prevalence of CSU is 0.78%.

Conclusion: This data presents the clinical profile of CSU patients. Patients reported a variety of comorbidities and a high proportion of patients required ER visits and hospitalizations which can have a significant economic impact.

Oral Berotralstat Treatment for 96 Weeks Consistently Reduces Hereditary Angioedema (HAE) Attack Rates Regardless of Baseline Attack Rate

Emel Aygoren-Pursun, Donald McNeil, Philip J. Collis, Bhavisha Desai, Dianne K. Tomita, Douglas T. Johnston on behalf of APeX-2 Study Investigators

Rationale: A goal of prophylactic HAE treatment is to reduce disease burden by decreasing attack rates. Berotralstat is a once daily (QD) prophylactic treatment for HAE. Here we report the long-term efficacy of berotralstat 150mg in patients who completed 96 weeks of treatment in the APeX-2 trial (NCT03485911), stratified by baseline attack rate.

Methods: Patients were randomized to berotralstat (110mg or 150mg) or placebo QD for 24 weeks. At Week 24, patients randomized to berotralstat continued on the same dose and placebo patients were re-randomized to berotralstat for an additional 24 weeks; after Week 48, all patients continued on berotralstat 150mg. Twenty-one patients completed a total of 96 weeks of berotralstat 150mg. This analysis evaluated patients by tertiles of baseline attack rate: Group 1: <2 attacks/month; Group 2: ≥2 to <3 attacks/month; Group 3: ≥3 attacks/month.

Results: In Group 1 (n=7), mean (SEM) monthly attack rate declined from 1.2(0.1) at baseline to 0.3(0.2) at Week 24, 0.1(0.1) at Week 48, and 0 at Week 96. In Group 2 (n=7), mean monthly attack rate declined from baseline 2.6(0.2) to 1.1(0.5) at Week 24, 0.1(0.1) at Week 48, and 0.3(0.2) at Week 96. In Group 3 (n=7), the mean attack rate declined from a baseline 4.6(0.6) to 1.7(0.8) at Week 24, 1.6(0.6) at Week 48, and 0.7(0.4) at Week 96. Over 70% of patients in each tertile had a ≥70% relative reduction in attack rate.

Conclusion: Regardless of baseline attack rate, berotralstat is an effective oral prophylactic treatment option that can reduce disease burden.

Berotralstat Demonstrates Low Hereditary Angioedema (HAE) Attack Rates in Patients Switching from Injectable Prophylaxis

Marc A. Riedl, William P. Sheridan, Lindsey J. Noble, Dianne Tomita, Daniel Soteres on behalf of APeX-S Study Investigators

Introduction: Berotralstat, an oral once-daily prophylactic treatment for HAE, is a FDA-approved effective alternative to injectable therapies. Here we report the safety and effectiveness in 34 patients who switched from injectable prophylactic therapy to berotralstat monotherapy at US sites in the open-label international APeX-S study (NCT03472040).

Methods: In the US all patients were allocated to berotralstat 150mg once daily (QD). Safety (primary objective), effectiveness and quality of life (secondary objectives) were evaluated. Per protocol patients were not required to discontinue and wash out previous injectable prophylactic treatment prior to enrollment.

Results: 34 patients discontinued lanadelumab (n=21), SC C1-INH (n=12), or IV C1-INH (n=1) and switched to berotralstat 150mg monotherapy. Mean monthly attack rates were consistently low following the switch to berotralstat. The mean (SD) monthly attack rate at Month 1 was 0.4 (0.8) which was sustained through Month 6 (0.4 [0.8]) and Month 12 (0.3 [0.7]). Median attack rates were 0.0 attacks/month during each timepoint throughout 12 months of treatment. Vomiting, diarrhea, and upper respiratory tract infection were the most common adverse events (each 11.8%) in this population following the switch to berotralstat, similar to the general study population.

Conclusion: The transition from injectable HAE prophylaxis to berotralstat 150mg QD was generally well tolerated. In addition, attack rates remained consistently low during 12 months of treatment indicating that patients switching to berotralstat monotherapy maintain good control of their HAE symptoms.

Mepolizumab Demonstrates Real-world Clinical Effectiveness in both Type 2 Biomarker High and Type 2 Biomarker Low Patients with Severe Asthma.

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Rationale: Mepolizumab, an anti-IL-5 monoclonal antibody, is a precision therapy for eosinophilic severe asthma. The mepolizumab RCTs in severe asthma suggested a baseline blood eosinophil threshold of 150 cells/μL to identify responders for beneficial exacerbation reduction response.

Methods: The applicability of this threshold was evaluated in two real-world experience data sets, REALITI-A, a prospective international database study (n=822) and REDES a retrospective national database study (n=318). Both studies were observational studies in adults with severe asthma in whom a physician had initiated treatment with mepolizumab 100 mg subcutaneous. The primary endpoint was the rate of clinically significant asthma exacerbations (CSE; requiring the use of systemic corticosteroids or hospital/emergency department admission) between the 12 months prior to (before treatment) and after initiating mepolizumab treatment. The CSE reduction in the year after starting mepolizumab was evaluated in relationship to categories of progressively increasing baseline pre-treatment blood eosinophil counts (cells/μL), with ranges from <150, through to ≥500 (REALITI-A) and <150 through to ≥700 (REDES).

Results: Mepolizumab significantly reduced total CSE in REALITI-A (with a 71% reduction) and REDES (77.5% reduction) from respective mean pre-treatment annual rates of 4.28 and 4.48. This reduction was evident across the spectrum of baseline blood eosinophil levels: REALITI-A, <150 n=96 (66%), ≥500 n=278 (75%) and REDES <150 n=25 (70%), ≥500-<700 n=61 (88%), ≥700 n=124 (81%).

Conclusions: These real-world studies identify that mepolizumab, as used by physicians, is effective in standard clinical care irrespective of type 2 eosinophil biomarker status (high or low) in patients with severe asthma.

Impact of Baseline Treatment, Duration of Disease, and Refractory Status on Outcomes in Mepolizumab-Treated Patients With EGPA

Paneez Khoury, Praveen Akuthota, Lee Baylis, Sarah Chang, Jane Bentley, Michael E Wechsler

Rationale: Mepolizumab, an anti-interleukin-5 monoclonal antibody has been shown to increase remission duration in patients with eosinophilic granulomatosis with polyangiitis (EGPA). We investigated impact of baseline treatment, disease duration, and refractory status on mepolizumab efficacy using Phase III MIRRA study data.

Methods: Patients with relapsing/refractory EGPA, receiving stable prednisolone/prednisone (≥7.5–≤50 mg/day), were randomized (1:1) to monthly mepolizumab 300 mg or placebo subcutaneously for 52 weeks. Co-primary endpoints were total accrued duration of remission from Weeks 0 to 52 and proportion of patients in remission at both Weeks 36 and 48. Data were stratified by baseline immunosuppressant (IS) use (yes/no) and disease duration (≤4/>4 years); analyses by baseline refractory disease status (yes/no) were performed post hoc.

Results: Of 136 patients enrolled in MIRRA, 72 had baseline IS use (placebo[n=31]/mepolizumab[n=41]), 70/136 had EGPA >4 years (placebo[n=36]/mepolizumab[n=34]) and 74/136 had refractory disease at baseline (placebo[n=40]/mepolizumab[n=34]). Mepolizumab increased accrued duration in remission versus placebo, irrespective of baseline IS use (odds ratio[95%CI]; yes:3.39[1.11,10.38]; no:11.85[3.50,40.13]), EGPA duration (odds ratio[95%CI]; ≤4 years:17.08[3.41,85.54]; >4 years:4.26[1.53,11.91]) or baseline refractory disease status (odds ratio[95%CI]; yes:3.70[1.29,10.65]; no:9.25[2.44,35.08]). More patients receiving mepolizumab were in remission at Weeks 36 and 48 versus those on placebo, irrespective of baseline IS use (yes:32%[13/41] vs 6%[2/31]; no:33%[9/27] vs 0%[0/37]), EGPA duration (≤4 years:24%[8/34] vs 0%[0/32]; >4 years:41%[14/34] vs 6%[2/36]), and baseline refractory disease status (yes:24%[8/34] vs 3%[1/40]; no:41%[14/34] vs 4%[1/28]).

Conclusions: In patients with EGPA, mepolizumab was associated with increased likelihood and duration of remission versus placebo, irrespective of baseline IS use, disease duration, and baseline refractory disease status.

The Impact of Comorbid Nasal Polyps on Real-World Mepolizumab Effectiveness in Patients With Severe Asthma: Results From the REALITI-A Study

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Introduction: Several Phase III clinical trials and open-label extension studies demonstrated that, in patients with severe eosinophilic asthma (SEA), mepolizumab reduces exacerbation rates, oral corticosteroid (OCS) use, and improves asthma symptoms. In previous studies, patients with SEA with nasal polyps (NP) demonstrated greater response to mepolizumab treatment than those without NP. This study assessed the impact of NP status on real-world mepolizumab effectiveness in patients with SEA.

Methods: REALITI-A, a 2-year observational study, enrolled adults with asthma newly prescribed mepolizumab treatment (100 mg subcutaneous). Patient-reported NP status (with/without) was recorded at enrollment. Primary endpoint: rate of clinically significant exacerbations (CSE; requiring systemic corticosteroids and/or hospital/ER admission) following mepolizumab treatment (follow-up) relative to the 12-month pre-treatment period; secondary endpoints: included change from baseline (28 days pre-mepolizumab) in daily maintenance OCS (mOCS) and total OCS (maintenance and rescue burst) dose during follow-up. This interim analysis assessed Week 53–56 outcomes, stratified by NP status at enrollment, in the full study population 1-year post mepolizumab treatment.

Results: Of 822 treated patients, 39% reported comorbid NP. Patients with NP experienced numerically greater reductions in rate of CSE at follow-up than those without NP (75% vs 69%). Both groups experienced reduced median mOCS dose; patients with NP experienced greater percent reductions versus patients without NP (83% vs 50%). Similarly, patients with NP experienced greater reductions in total OCS dose versus those without NP (68% vs 51%). By Week 53–56, more patients with NP had improved mOCS/total OCS use, or discontinued use altogether, than those without NP.

Conclusions: This real-world study showed that mepolizumab reduced exacerbations and OCS use in patients with SEA, with greater impact in patients with comorbid NP. Patients with SEA and NP represent a clinically identifiable phenotype particularly suited to mepolizumab therapy.

International, prospective real-world study of mepolizumab in patients with severe asthma at one year: REALITI-A

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Introduction: Mepolizumab improves asthma control in patients (pts) with severe asthma in clinical trials, but real-world data is limited.

Aim: To assess real-world clinical outcomes in pts initiating mepolizumab treatment.

Methods: REALITI-A is a 2y, international, prospective, single-arm, observational cohort study enrolling pts with severe asthma, newly prescribed mepolizumab 100mg SC. 1y pre-exposure exacerbation data availability was a prerequisite. Primary endpoint: rate of clinically significant exacerbations (CSEs; requiring oral corticosteroids [OCS] and/or emergency room [ER] visit/hospitalisation). Exacerbations requiring ER visit/hospitalisation and maintenance OCS (mOCS) were key secondary endpoints; investigator-determined treatment-related adverse events (TRAEs) were collected. Our interim analysis includes all pts at 1y follow-up (median 366days).

Results: 822 treated pts included (mean age, 54.0y; 63% female; geometric mean blood eosinophil count, 353cells/µL; smoker: former/current 40%, never 60%; 39% on mOCS). CSEs reduced from 4.28 (pre-) to 1.23 (post-exposure) events/y (RR: 0.29 [95%CI 0.26,0.32]). Exacerbations requiring hospitalisation/ER visits reduced from 0.95 to 0.23 events/y (RR: 0.24 [0.20,0.29]). mOCS dose data were available for 298 (baseline) and 222 (wk53–56) pts. Median mOCS dose reduced from 10 (baseline) to 2.5mg/day at wk53–56; 43% (95/222) stopped mOCS by wk53–56. 85 (10%) pts had on-treatment TRAEs, 6 (<1%) serious on-treatment TRAEs; 1 fatal (hepatic cancer).

Conclusions: This real-world study of mepolizumab in pts with severe asthma shows clinical effectiveness with marked reductions in CSE and mOCS use.

Improvement in Patient-Reported 'Taste' and Association with Smell in Dupilumab-Treated Severe Chronic Rhinosinusitis with Nasal Polyps Patients From the SINUS-24 and SINUS-52 Trials

Peters AT, Soler ZM,[2] Kern RC, Lane AP, Nash S

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is associated with high symptom burden. Loss of patient-reported 'taste' is common in CRSwNP and is associated with loss of smell. This post hoc analysis evaluated the impact of dupilumab 300 mg q2w on patient-reported 'taste' and associations between 'taste' and smell in the phase 3 SINUS-24 and SINUS-52 trials (NCT02912468/NCT02898454).

Methods: Patient-reported 'taste' was assessed weekly using a loss-of-'taste' severity scale (0-3, higher score = greater severity). Scores were analyzed in the intention-to-treat (ITT) and an enriched population (baseline loss-of-'taste' severity >0) to adjust for patients not reporting any loss-of-'taste'. Associations between 'taste' severity and smell (loss-of-smell score [LoS], University of Pennsylvania Smell Identification Test [UPSIT], and 22-item Sino-Nasal Outcome Test [SNOT-22] smell/taste item), were assessed using Spearman's rank.

Results: Patient-reported loss-of-'taste' improved in dupilumab-treated patients vs placebo in the ITT populations of SINUS-24 (n = 143/133 dupilumab/placebo; least-squares [LS] mean difference [95% CI] -0.94 [-1.14, -0.74]; $P < 0.0001$) and SINUS-52 (n = 295/153; -0.77 [-0.95, -0.59]; $P < 0.0001$) at Week 24. Similar improvements were observed in the enriched populations (SINUS-24: n = 123/121; -0.99 [-1.21, -0.78]; SINUS-52: n = 262/144; -0.80 [-0.98, -0.62]; all $P < 0.0001$). A greater proportion of dupilumab than placebo patients achieved ≥ 1 point improvement in loss-of-'taste' severity at Week 24 (61% vs 26%; pooled studies ITT; $P < 0.0001$]), maintained at Week 52. Moderate associations were observed between improvement in loss-of-'taste' severity and in LoS, UPSIT, and SNOT-22 smell/taste item scores in the pooled ITT population at Week 24 (0.56, -0.39, and 0.58, respectively, all $P < 0.0001$) and maintained at Week 52.

Conclusions: In patients with severe CRSwNP, dupilumab improved smell and patient-reported 'taste' vs placebo. This finding is consistent with the known central role of smell in 'taste'.

Tralokinumab treatment modifies stratum corneum lipid composition in skin of adolescents with atopic dermatitis

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Background: In atopic dermatitis (AD), Th2 cytokines, including interleukin (IL)-13, alter skin lipid metabolism. Tralokinumab is a high-affinity, monoclonal antibody that neutralizes IL-13.

Objective: We evaluated effects of tralokinumab on stratum corneum (SC) lipid composition in adolescents with moderate-to-severe AD (ECZTRA 6, NCT03526861).

Methods: Adolescents (age 12-17) were randomized to subcutaneous tralokinumab 150mg, 300mg every 2 weeks, or placebo. Primary endpoints were IGA 0/1 and EASI-75 at Week 16. Tape strip samples were collected for SC lipid and transcriptomics analyses in lesional and non-lesional skin while ceramides, sphingomyelins and natural moisturizing factor (NMF) components were quantified using targeted LC-ESI-MS/MS.

Results: At Week 16, greater proportions of patients receiving tralokinumab achieved IGA 0/1 (150mg/300mg 21.4%/17.5% vs placebo 4.3%; $P<0.001/P=0.002$), and EASI-75 (28.6%/27.8% vs 6.4%; $P<0.001/P=0.001$). At baseline, key NMF components, urocanic acid (UCA) and 2-pyrrolidone-5-carboxylic acid (PCA), and barrier lipid omega-acyl ceramide (EOS-CER) were significantly downregulated in lesional vs non-lesional skin while short-chain NS-ceramide (NS-CER) and sphingomyelin levels were upregulated. Tralokinumab substantially increased NMF content and improved lipid composition by increasing EOS-CER content and proportion of NS-CER with long-chain fatty acids while decreasing sphingomyelins.

Conclusions: Tralokinumab improved AD severity and shifted skin NMF and lipid parameters from a lesional to non-lesional skin profile, demonstrating the effectiveness of neutralizing IL-13 in improving the skin barrier, evidenced by shifts in lipids of importance for maintaining intact SC structure.

Long-term treatment with tralokinumab normalizes the molecular gene signature of atopic dermatitis

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Introduction: Interleukin (IL)-13 is a key driver of skin inflammation and barrier abnormalities in atopic dermatitis (AD). Tralokinumab is a high-affinity, monoclonal antibody that specifically neutralizes IL-13. Tralokinumab demonstrated efficacy and safety for AD treatment in pivotal phase 3 trials at Week 16, and high levels of EASI-75 and IGA 0/1 response were sustained through 2 years of continued treatment. The impact of long-term tralokinumab treatment on the molecular phenotype of AD skin has not been previously assessed. We investigated the impact of IL-13 neutralization on skin biomarkers following 2 years of tralokinumab treatment in patients with moderate-to-severe AD in the Phase 3 ECZTRA 1 (NCT03131648) trial and the long-term extension trial ECZTEND (NCT03587805).

Methods: Skin biopsies (n=13 subjects) were collected from lesional (baseline, Week 16, and Week 104) and non-lesional skin (baseline and Week 104). Gene expression levels of biomarkers related to inflammation and skin barrier integrity were assessed by RNA sequencing and validated by qPCR. Treatment differences were estimated by linear mixed effect models with treatment and time as fixed effects and random effects for each patient.

Results: Two years of tralokinumab treatment shifted the transcriptomic profile of lesional skin towards that of non-lesional skin; this shift was larger than that seen at Week 16. These shifts included genes related to the Th2, Th17, and Th22 pathways, as well as epidermal barrier. A strong shift was also observed in atherosclerosis signaling pathway genes. At 2 years, tralokinumab treatment also modified the transcriptomic profile of the non-lesional skin, improving the subclinical disease seen at baseline in normal-appearing skin.

Conclusions: These shifts in the cutaneous biomarker profile highlight the role of IL-13 as a key driver of the AD molecular signature, and support the role of targeted biologic therapy for long-term AD management.

Reaction after COVID-19 mRNA Booster Vaccination

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Introduction: With the continued plight against Coronavirus disease (Covid-19), vaccination has been tremendously advantageous in combatting this virus. As the vaccination campaign continues, adverse reactions emerge. Although immediate reactions gain more attention with the initial 2 doses, we report a delayed urticarial reaction with only the Booster dose of Covid-19 mRNA vaccination.

Case Description: A healthy 43 year old male received the BioNTech BNT162b2 mRNA Covid-19 Booster vaccine on December 12, 2021. He had received the 1st and 2nd doses of the vaccine and experienced no adverse effects. However, five days after the Booster vaccine, patient developed a global generalized urticarial reaction. He had widespread urticarial areas with erythematous rashes and maculopapular wheals. The patient described the rash as 'jumping' in location. The rash was intensely pruritic causing sleep deprivation. The urticarial lesions were all over, but seemed to favor 'hot spots' of the body, ie, axilla, waist, groin areas. There was no associated angioedema, shortness of breath, or wheeze. Skin biopsy was consistent with urticaria. The patient was eventually started on antihistamines which needed to be titrated up significantly. His regimen for controlling the urticaria included Fexofenadine 180 mg 2 tablets twice a day, Famotidine 20 mg 1 tablet twice a day, and Hydroxyzine 50 mg 2 tablets at bedtime. The patient required this regimen for up to 4 months after the Booster vaccine to help control the chronic spontaneous urticaria.

Conclusion: This case illuminates a delayed urticarial reaction post COVID-19 Booster vaccination. This case prompts awareness to find other patients who may have had similar reactions and also help the medical community develop a management protocol to control the hives and furthermore, perhaps a protocol prior to future booster shots if needed.

Summit: A 3-Part, Phase 2 Study of Bezuclastinib (CGT9486), an Oral, Selective and Potent KIT D816V Inhibitor, in Adult Patients with NonAdvanced Systemic Mastocytosis (NonAdvSM)

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Background: Systemic mastocytosis (SM) is characterized by mast cell infiltration of extracutaneous tissue and a spectrum of diagnoses from non-advanced to advanced disease. Approximately 80-85% of SM patients are diagnosed with indolent SM (ISM) and 5% with smoldering SM (SSM). There are no FDA approved therapies to treat ISM or SSM, leaving anti-mediator therapies for symptom control with variable effectiveness and tolerability. The molecular pathogenesis is driven by KIT D816V mutations in 95% of SM patients. Agents targeting this kinase have shown off-target kinase activity which may limit dosing and efficacy. Bezuclastinib was designed to target KITmutations (e.g., D816V) with high potency and specificity while avoiding other kinases with known liabilities. Bezuclastinib has demonstrated minimal brain penetration and no CNS toxicities in preclinical studies. Clinical activity has been observed in patients with advanced solid tumors including locally advanced, unresectable, or metastatic gastrointestinal stromal tumors (GIST); with reduction in KIT exon 17 mutational burden, and a temporally associated reduction in tumor burden, supporting the investigation of bezuclastinib in KIT-driven diseases.

Methods: The Summit study (NCT05186753) is a multi-center, Phase 2, double blind, placebo-controlled, 3-part clinical study to evaluate the safety, efficacy, and biomarker correlates of the KIT inhibitor bezuclastinib in patients with ISM and SSM. This study will enroll patients with ISM or SSM who have inadequate control of their symptoms despite at least 2 anti-mediator therapies. Part 1 is intended to determine the recommended dose of bezuclastinib. In Part 2, subjects will be randomized to placebo or bezuclastinib, in combination with best supportive care (BSC). In Part 3, patients who have completed treatment in Part 1 or Part 2 of the study may participate in a long-term extension and receive open-label bezuclastinib in combination with BSC.

Conclusions: Data from this study will support development of bezuclastinib in SM.

Hematologic Laboratory Parameters in Adults and Children Aged 6 Months to 18 Years With Moderate-to-Severe Atopic Dermatitis treated with Dupilumab

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Background: Systemic treatments for atopic dermatitis (AD) often necessitate laboratory monitoring. Here, we further characterize the safety of dupilumab by evaluating hematology parameters across patients with moderate-to-severe AD aged 6 months to ≥18 years.

Methods: We report hematology parameters from patients with moderate-to-severe AD who participated in any of four randomized, placebo-controlled, phase 3 studies: LIBERTY AD PRESCHOOL (6 months to 5 years; NCT03346434 part B); dupilumab 200/300mg every 4 weeks (q4w) + topical corticosteroids (TCS; n=83) or placebo +TCS (n=79). LIBERTY AD PEDS (6–11 years; NCT03345914); pooled dupilumab +TCS (100/200mg q2w +TCS [n=122]; 300mg q4w +TCS [n=120]) or placebo + TCS (n=120). LIBERTY AD ADOL (12–17 years; NCT03054428); pooled dupilumab (200/300mg q2w [n=82]; 300mg q4w [n=83]) or placebo (n=85). LIBERTY AD CHRONOS (≥ 18 years; NCT02260986) pooled dupilumab (300mg q2w + TCS [n=110]; 300mg qw +TCS [n=315]) or placebo +TCS (n=315).

Results: The greatest mean change (SD) from baseline in platelet count was observed at Week 16 in the ≥18-years group (dupilumab: -26.6×10^9/L [55.4], placebo: -14.7×10^9/L [45.3]). The greatest mean change from baseline in eosinophil count was observed at Week 4 (0.48×10^9/L [1.8]) in the 6-months to 5-years dupilumab treatment group, which trended downwards by Week 16 (0.31×10^9/L [1.4]). Mean change (SD) in eosinophil count remained minimal in all placebo treatment groups. The greatest mean changes noted here were not clinically significant. 1 patient in the ≥18-years placebo group reported a TEAE of neutropenia that led to treatment discontinuation. Overall safety was consistent with the known dupilumab safety profile.

Conclusions: No clinically meaningful changes in hematology parameters were observed during dupilumab treatment in patients with moderate-to-severe AD, highlighting that no routine laboratory monitoring for hematology parameters is required during dupilumab treatment of pediatric or adult patients.

Treatment of autoimmune inner ear disease with canakinumab

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Introduction: Autoimmune inner ear disease (AIED) is one of the few forms of sensorineural hearing loss that can be treated by medical therapy, a fact that emphasizes the importance of early recognition. We report one subject who was successfully treated with canakinumab.

Case Presentation: The patient was a sound engineer who presented to the Allergy & Immunology Clinic with bilateral hearing loss associated with vertigo and had been diagnosed with autoimmune inner ear disease. He was on a regimen of acyclovir, famciclovir, hydroxychloroquine, and prednisone 30 mg daily and noted to have side effects of long-term prednisone use. It was decided to try immunomodulators with the goal of reducing the need for prednisone. He was trialed on mycophenolate mofetil, azathioprine, methotrexate, and tacrolimus, none of which allowed for reduction in prednisone. Further literature search suggests evidence that IL-1β is elevated in patients with steroid-resistant AIED and that Anakinra, an IL-1β receptor antagonist that requires subcutaneous daily dosing, was effective in 14 AIED steroid non-responders. Canakinumab is a selective human monoclonal antibody that blocks IL-1β and requires dosing only once every 4-8 weeks. Therefore, it was decided to start off-label use of canakinumab which resulted in significant hearing improvement 1 week after infusion and lasted for about 6-7 weeks. He now receives injections every 6 weeks and resumed working as a sound engineer.

Discussion: Improvement with the use of canakinumab in this patient suggests an immune-mediated etiology for his hearing loss. This supports the argument for early consideration of biologic use in AIED especially in a condition in which the timing of irreversible hearing loss is unpredictable. Early initiation of biologic use can preclude the use of glucocorticoids and other cytotoxic medications that have higher toxicity. Further studies are needed to validate the efficacy of canakinumab use in AIED.

Comparing effects of the COVID-19 Pandemic on Patients with Pathogenic Variant of Nuclear Factor Kappa B Subunit 1 (NFKB1) and Cytotoxic T Lymphocyte Antigen 4 (CTLA4)

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Background: Clinical presentation and immune responses to infection and/or immunization to SARS-CoV-2 may depend on the underlying genetic defects, progression of immune dysregulation, and comorbidities. We compared disease and immune response to SARS-CoV-2 in a cohort of patients with NFKB1 and CTLA4 deficiencies at our tertiary medical center.

Methods: We performed retrospective chart review and telephone interviews of genetically-confirmed NFKB1 and CTLA4 deficient patients for demographic information, clinical history, SARS-CoV-2 vaccination/infection, symptoms, antibody response, and comorbidities.

Results: Our patient cohort included 3 children and 5 adults (median age 21.5 years, range 15-51) (CTLA4 cohort) and 1 child and 6 adults (median age 26 years, range 17-52) (NFKB1 cohort), from 5 families. All patients were on immunoglobulin replacement therapy (IgRT) except two asymptomatic children with CTLA4 and one adult with NFKB1. Seventy-five percent of patients were vaccinated in each cohort. COVID infection occurred in 37.5% of CTLA4 and 50% of NFKB1 cohorts. One adult from each cohort received monoclonal antibodies with good response. Hospitalization was required for a 42-year-old patient with NFKB1 deficiency, hypogammaglobulinemia (low compliance on IgRT), moderate persistent asthma, and obesity (BMI 30). All infected patients were unvaccinated. SARS-CoV-2 spike IgG antibody levels were assessed in 50% of cases. It was fully absent in 4 of 4 NFKB1 deficient adult patients, it was preserved in an asymptomatic child, and absent to low in 3 of 4 CTLA4 deficient adults. Patients who received monoclonal antibody therapy have not yet been tested.

Conclusions: Most NFKB1 and CTLA4 patients did well during this pandemic except for one NFKB1 patient with low compliance and comorbidities. Antibody response to the SARS-CoV-2 vaccine and/or infection were low to absent except for an asymptomatic child. The contribution of underlying gene defects, progression of antibody deficiency/immune dysregulation, and comorbidities to the risk of severe infection are yet to be determined

A Patient with Hereditary Angioedema (HAE) with Normal C1-INH, and Systemic Lupus Erythematosus with Pregnancy

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Case Report: A 24-year-old female patient with Hereditary Angioedema (HAE), normal C1-esterase inhibitor with pregnancy.

Case Description: A 24-year-old, Caucasian female, with history of recurrent attacks of angioedemathat started at the age of 12. The swelling affects her face, tongue, lips, larynx, and extremities. At the age of 19, the patient developed SLE, started on oral corticosteroid and Azathioprine. She continued to have recurrent episodes of angioedema. She has no history of ACE inhibitor use, and no family history of angioedema.

Lab Results: C1-INH antigen*: 27 mg/dL (15-35 mg/dL), C1-INH function: 69.7% (70-130), C2 complement level*: 3.1 mg/dL (1.6-4.0 mg/dL), C4 complement level*: 32 mg/dL (10-40 mg/dL), C1q level:18 mg/dL (12-22 mg/dL), negative C1q Binding assay, ANA: Positive (1/80 homogenous), Anti-dsDNA: Positive, P-ANCA: Positive.
*Repeated levels during attacks were within normal levels.

Course During Pregnancy: Throughout the patients' pregnancy, the episodes became more frequent and severe. To note, the patient didn't have access to any of the HAE novel therapeutic agents until the start of the labor process. During labor, the patient developed an acute attack of tongue swelling, laryngeal edema, and vaginal swelling. She was promptly treated with Icatibant subcutaneously, which aborted the attack. Then, she was given Human C1-INH 2000 IU, subcutaneously. The patient had normal vaginal delivery, and a healthy full term male baby. She had several acute attacks in the early post-partum period which were treated successfully with Icatibant. Breast feeding was stopped, and **Human C1-INH 2000 IU twice weekly was started, currently doing well with no significant episodes.**

Discussion: We report a case of HAE with normal C1-INH1, SLE with normal pregnancy and delivery course. The use of Icatibant, a bradykinin receptor blocker, was effective in aborting angioedema. The patient is currently doing well on Human C1-INH 2000 IU twice weekly.