

Eastern Allergy Conference

August 16-18, 2020 ~ Palm Beach, FL

All Scientific Posters will be on display in the Ponce Exhibit Hall 1, 2, & 3, during the coffee breaks, 10:00 -10:45am, Monday, August 17 and Tuesday, August 18, 2020.

Not for
CME Credit

Dupilumab significantly improves atopic dermatitis in children aged ≥ 6 to <12 years: Results from Phase 3 Trial (LIBERTY AD PEDS)

Melinda Gooderham, Lisa A. Beck, Mark Boguniewicz, Lawrence Sher, Jamie Weisman, Ashish Bansal, Naimish Patel, Xian Sun, Bethany Beazley and Brad Shumel

Background: Dupilumab is approved in the USA for subcutaneous administration every 2 weeks (q2w) for the treatment of patients aged ≥ 12 years with moderate-to-severe atopic dermatitis (AD) inadequately controlled with topical prescription therapies or when those therapies are not advisable. We present dupilumab efficacy and safety data in children aged ≥ 6 to <12 years with severe AD.

Methods: In this double-blind trial (NCT03345914), children aged ≥ 6 to <12 years (minimum weight 15kg) with severe AD (Investigator's Global Assessment [IGA] score=4) were randomized 1:1 to subcutaneous dupilumab q2w (100mg if baseline weight <30 kg, 200mg if ≥ 30 kg), every 4 weeks (q4w, 300mg regardless of weight), or placebo for 16 weeks. From Day -14, all patients initiated standardized treatment with medium-potency topical corticosteroids (TCS).

Results: 367 patients were randomized (q2w/q4w/placebo groups, n=122/n=122/n=123). At Week 16, 29.5%/32.8%/11.4% of patients receiving q2w/q4w/placebo achieved IGA scores of 0/1 (clear/almost clear); 67.2%/69.7%/26.8% achieved $\geq 75\%$ improvement from baseline in Eczema Area and Severity Index (EASI). Least squares (standard error) mean percent change in EASI and Peak Pruritus Numerical Rating Scale were $-78.4(2.35)/-82.1(2.37)/-48.6(2.46)$ and $-57.0(2.77)/-54.6(2.89)/-25.9(2.90)$, respectively ($P<0.001$ vs placebo for all comparisons). Serious adverse events (AEs) and AE-related treatment discontinuations were rare; injection-site reactions and conjunctivitis were more common with dupilumab than with placebo.

Conclusion: Dupilumab+TCS showed clinically meaningful and statistically significant improvement in AD signs and symptoms in children aged ≥ 6 to <12 years with severe AD and was well tolerated with no new safety signals compared with adults and adolescents.

Funding: Sanofi/Regeneron

Dupilumab treatment effects are observed after the first dose across atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyps: Data from Phase 3 SOLO 1 & 2, LIBERTY ASTHMA QUEST, and SINUS-52 Studies

G. Walter Canonica, Anju T. Peters, Martin DesRosiers, Eric L. Simpson, Megan S. Rice, Zhen Chen, Abhijit Gadhari, Leda P. Mannent, Yamo Deniz, Paul Rowe, Nikhil Amin

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. This analysis of phase 3 studies in atopic dermatitis (AD; SOLO 1 [NCT02277743] & SOLO 2 [NCT02277769]), asthma (LIBERTY ASTHMA QUEST [NCT02414854]), and chronic rhinosinusitis with nasal polyps (CRSwNP; SINUS-52 [NCT02898454]) evaluates the effect and onset of action of dupilumab, administered every 2 weeks (q2w), after the first dose, prior to the second dose at Week 2 (W2) in patients across these type 2 driven diseases.

Methods: In SOLO 1 and 2 pooled, least squares (LS) mean percentage change from baseline in Eczema Area and Severity Index (EASI) score at W2 was assessed in moderate-to-severe AD patients treated with dupilumab 300mg q2w or placebo weekly. In QUEST, LS mean change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV₁) at W2 was assessed in uncontrolled, moderate-to-severe asthma patients treated with dupilumab 200mg/300mg q2w, or matched placebo. In SINUS-52, LS mean change from baseline in the University of Pennsylvania Smell Identification Test (UPSIT) score at W2 was assessed in severe CRSwNP patients treated with dupilumab 300mg q2w or placebo.

Results: In AD, dupilumab vs placebo significantly improved EASI scores at W2 (-34.4% vs -11.1% ; LS mean difference [95% CI]: -23.2% [$-27.50, -18.99$]; $P<0.0001$). In asthma, dupilumab 200mg/300mg q2w vs placebo significantly improved FEV₁ at W2 (0.25L/0.28L vs 0.11L/0.13L; LS mean difference [95% CI]: 0.14L [0.09-0.19]/0.15L [0.10-0.20]; both $P<0.0001$). In CRSwNP, dupilumab vs placebo significantly improved UPSIT scores at W2 (6.34 vs 0.98; LS mean difference [95% CI]: 5.36 [3.62-7.10]; $P<0.0001$). Dupilumab was generally well tolerated.

Conclusions: Dupilumab exhibits consistently rapid onset of action across multiple type 2 inflammatory diseases, with significant improvement noted after the first dose.

Funding: Sanofi/Regeneron

Dupilumab efficacy in GINA-defined difficult-to-treat type 2 asthma patients

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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. In phase 2b (P2) (NCT01854047) and phase 3 (P3) QUEST (NCT02414854), add-on dupilumab 200mg and 300mg every 2 weeks (q2w) vs placebo reduced severe exacerbations and improved pre-bronchodilator forced expiratory volume in 1 second (FEV₁) in patients with uncontrolled, moderate-to-severe asthma. Treatment effects were greater in patients with elevated baseline type 2 biomarkers (baseline blood eosinophils and fractional exhaled nitric oxide [FeNO]). The recently published GINA guidelines for difficult-to-treat and severe asthma specifies baseline blood eosinophils ≥ 150 cells/ μ L and/or baseline FeNO ≥ 20 ppb as cut-offs to define type 2 inflammatory asthma. This analysis assessed dupilumab efficacy in patients with baseline eosinophils ≥ 150 cells/ μ L or baseline FeNO ≥ 20 ppb.

Methods: Annualized severe exacerbations during the 24-week (P2) and 52-week (P3) treatment periods and change from baseline in pre-bronchodilator FEV₁ (L) at Week 12 were assessed.

Results: Dupilumab 200mg/300mg q2w vs placebo significantly reduced severe exacerbations in patients with eosinophils ≥ 150 cells/ μ L by 72%/73% in P2, and by 56%/60% in P3, respectively, and in those with baseline FeNO ≥ 20 ppb by 70%/80% in P2 and by 65%/58% in P3 (all $P<0.01$). Dupilumab 200mg/300mg q2w also significantly improved pre-bronchodilator FEV₁ in patients with eosinophils ≥ 150 cells/ μ L by 0.23L/0.18L in P2, and by 0.17L/0.15L in P3, respectively, and in patients with FeNO ≥ 20 ppb, by 0.22L/0.20L in P2, and by 0.22L/0.20L in P3, respectively (all $P<0.01$). Overall, the most frequent adverse events were upper respiratory tract infection (P2: 15%/13% vs 18%) and injection-site reaction (P3: 15%/18% vs 5%/10%) in dupilumab vs placebo groups, respectively.

Conclusion: Dupilumab showed consistent efficacy in patients with difficult-to-treat type 2 asthma as defined by GINA cut-offs for type 2 inflammatory biomarkers.

Funding: Sanofi/Regeneron

Dupilumab decreases blood biomarkers in adolescents with moderate-to-severe atopic dermatitis: Data from a Phase 3 Trial (LIBERTY AD ADOL)

Eric L. Simpson, Hiroyuki Fujita, Kazuhiko Arima, Jennifer Hamilton, Ana B. Rossi, Ashish Bansal

Background: Dupilumab is approved in the USA for subcutaneous administration every 2 weeks for the treatment of patients (pts) aged 12 years and older with moderate-to-severe atopic dermatitis (AD) inadequately controlled with topical prescription therapies or when those therapies are not advisable. Here, we evaluate blood levels of type 2 inflammatory markers in pts from a randomized, double-blind, placebo (PBO)-controlled, phase 3 trial of dupilumab in adolescents with moderate-to-severe AD inadequately controlled by topical therapies (NCT03054428).

Methods: 251 pts aged ≥ 12 to <18 years were randomized 1:1 to subcutaneous dupilumab every 2 weeks (q2w; 200mg/300mg), every 4 weeks (q4w; 300mg), or PBO q2w, for 16 weeks. Blood samples for biomarker analysis (thymus and activation-regulated chemokine [TARC], total IgE, allergen-specific IgE and lactate dehydrogenase [LDH]) were collected.

Results: Baseline (BL) biomarker levels were similar across treatment groups. At Week 16 (Wk16), TARC decreased by a median (interquartile range [IQR]) of -2424.0 (-5966.0 ; -562.0), -1541.0 (-4669.0 ; 685.0), and -220.0 (-864.0 ; 470.0) pg/mL for q2w, q4w and PBO, respectively (nominal $P<0.0001$ vs PBO). Total IgE decreased by a median (IQR) of -2015.0 (-5264.0 ; 929.0), -1658.0 (-5321.0 ; 279.5) and increased by 22.0 (-661.0 ; 1124.0) kU/L with q2w, q4w and PBO, respectively at Wk16 (nominal $P<0.0001$ vs PBO). Dupilumab also reduced allergen-specific IgE concentrations for food/aero-allergies (nominal $P<0.0001$ for all allergens at Wk16). LDH concentrations at Wk16 decreased by a median (IQR) of -57.5 (-124.5 ; 20.5), -80.5 (-120.0 ; 28.0) and increased by 3.5 (-26.5 ; 30.0) U/L for q2w, q4w and PBO, respectively (nominal $P<0.0001$ vs PBO).

Conclusions: Dupilumab treatment for 16 weeks resulted in marked reduction in blood levels of multiple type 2 inflammatory biomarkers and LDH, which accompanied previously reported effect in improving AD signs and symptoms.

Funding: Sanofi/Regeneron

Classification of asthma severity and measurement of asthma control improve asthma outcomes in a pediatric primary care setting

Kate Krueck MD, William Long MD and Susan Mills RRT

Introduction:

Though complications of asthma are largely preventable, emergency department (ED) visits and hospitalizations for pediatric asthma still occur with regular frequency. Understanding which asthma patients are at higher risk for these outcomes would help primary care physicians stratify patients for escalation of care. Further, tools that more accurately reflect airway impairment enable a more precise assessment of asthma control to better guide asthma management.

Methods:

Following a concerted effort to accurately classify patients with asthma by severity of disease, we measured ED visits and hospital admissions attributable to asthma for patients classified with intermittent versus persistent asthma. We implemented tools designed to assess asthma control, including pulmonary function testing (PFT) to measure airway obstruction, fractional exhaled nitric oxide (FeNO) to measure airway inflammation, and the Asthma Control Test (ACT) to measure asthma symptoms, and compared rates of utilization of these tools to rates of asthma related ED visits and hospital admissions.

Results:

Patients classified with persistent asthma had substantially higher rates of asthma related ED visits and hospitalizations compared to patients classified with intermittent asthma. Rates of measurement of PFTs, measurement of FeNO, and utilization of ACTs correlated with a reduction in all asthma related hospital admissions, but did not correlate with all asthma related ED visits. Intermittent asthma patients saw a reduction of ED visits, whereas persistent asthma patients did not see a consistent correlation.

Conclusions:

Using asthma severity to predict risk of adverse pediatric asthma outcomes allows physicians to use population health strategies to implement more intensive asthma monitoring for those patients at highest risk. This double tiered strategy correlates with a reduction in pediatric asthma related hospital admissions. Avoidance of this adverse outcome has been shown to improve quality of life measures and reduce asthma related health care costs.

Once-daily, single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI in inadequately controlled asthma: The CAPTAIN study

Ian Pavord, Guy Peachey, Huib Kerstjens, Edward Kerwin, Robert Nathan, Nicola A. Hanania, Steven Pascoe, Andrew Fowler, Zelig Bailes, Dawn Edwards, Neal Sule, Neil Barnes, Louis-Philippe Boulet, Maggie Tabberer, Laurie A. Lee

Introduction: Approximately 50% of asthma patients have inadequately controlled symptoms despite inhaled corticosteroid/long-acting β_2 -agonist therapy.

Methods: Phase IIIA, randomized, double-blind, 24–52 week, parallel-group study in adults with asthma with pre-bronchodilator FEV₁ <85% and Asthma Control Questionnaire (ACQ-6) score \geq 1.5. Treatment: once-daily fluticasone furoate/vilanterol (FF/VI, 100/25, 200/25 mcg) or FF/umeclidinium (UMEC)/VI (100/31.25/25, 100/62.5/25, 200/31.25/25, 200/62.5/25 mcg) via Ellipta inhaler. Endpoints: mean change from baseline in trough FEV₁ at Week 24 (primary), annualized moderate/severe asthma exacerbation rates, proportion of ACQ-7 and St George's Respiratory Questionnaire (SGRQ) responders (Week 24). Safety was assessed. FF doses were pooled for non-lung function endpoints for each UMEC dose.

Results: In the intent-to-treat population (n=2436), FF/UMEC 62.5 mcg/VI statistically significantly improved trough FEV₁ versus FF/VI for each corresponding FF dose (100/62.5/25 mcg vs FF/VI 100/25 mcg: 110 mL [95% CI: 66, 153], 200/62.5/25 mcg vs FF/VI 200/25 mcg: 92 mL [95% CI: 49, 135]; all p<0.001). FF/UMEC 31.25 mcg/VI showed nominally statistically significant improvements in trough FEV₁ (100/31.25/25 mcg vs FF/VI 100/25 mcg: 96 mL [95% CI: 52, 139]; 200/31.25/25 mcg vs FF/VI 200/25 mcg: 82 mL [95% CI 39, 125]). Numerical reduction in exacerbation rate observed for FF/UMEC 62.5 mcg/VI versus FF/VI (rate ratio [95% CI]: 0.87 [0.72, 1.05]). ACQ-7 responder rates were greater for FF/UMEC 62.5 mcg/VI versus FF/VI (63% vs 55%; OR 1.43; 95% CI: 1.16, 1.76); there were no differences in SGRQ responder rates (69%, vs 66%; OR 1.14; 95% CI: 0.92, 1.42). FF/UMEC/VI safety profile was similar to FF/VI.

Conclusions: Dual bronchodilation effects are additive in asthma. FF/UMEC 31.25 and 62.5 mcg/VI provided statistically significant increases in lung function versus FF/VI. FF/UMEC 62.5 mcg/VI improved asthma control versus FF/VI in asthma patients inadequately controlled on ICS/LABA.

Funding: GSK (study 205715/NCT02924688).

Reprinted from Journal of Allergy and Clinical Immunology, 145(2 Suppl), Pavord I, Peachey G, Kerstjens H, Kerwin E, Nathan R, Hanania N, Pascoe S, Fowler A, Bailes Z, Edwards D, Sule N, Barnes N, Boulet LP, Tabberer M, Lee L, Once-daily, single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI in inadequately controlled asthma: the CAPTAIN study, AB241, Copyright 2020, with permission from Elsevier.

Benefit of dupilumab in treatment-refractory ABPA

Matthew J. Nugent, Reece A. Jones MD

Rationale: Allergic Bronchopulmonary Aspergillosis (ABPA) involves a marked inflammatory response to the ubiquitous mold *Aspergillus fumigatus* (AF) in patients with asthma or cystic fibrosis. Treatment options include traditional asthma therapy, systemic steroids, oral antifungals, and omalizumab, yet control can still be elusive. Evidence that T cell activation may be central to the immunopathophysiology of ABPA1 suggest a possible role for dupilumab, a monoclonal antibody directed against the alpha subunit of the IL4-Receptor, for refractory cases, but there is little clinical data evaluating this.

Methods: We present a patient with ABPA (asthma, centrolobular bronchiectasis, AF-specific IgE on ST and ELISA, IgE 2000-3000 IU/mL, Bronchoalveolar lavage [BAL] culture positive for AF with BAL eosinophilia, peripheral eosinophilia 800-1000/uL, evaluations and treatments at National Jewish and UC Davis Medical Centers) who was prednisone-dependent \geq 20 mg/day despite years of co-treatment with omalizumab, having failed itraconazole, intolerant of benralizumab, who responded significantly to dupilumab.

Results: Benefit demonstrated by elimination of systemic steroid (tapered to zero over 2 weeks after starting dupilumab) alongside a 12-week improvement in Asthma Control Test (ACT) score of 9 (from 12 to 21) and pre-bronchodilator FEV₁ increase of 11% (0.16L), >50% reduction of total IgE to 640 from baseline ~2000 ku/L. This clinical improvement, sustained over 3 months, is the patient's longest systemic steroid-free period in years.

Conclusions: Dupilumab demonstrated efficacy in this case, and may represent a potential therapeutic consideration for patients with refractory ABPA.

Step-up to high dose fluticasone furoate in combination with long-acting bronchodilator in inadequately controlled asthma: The CAPTAIN study

Nicola A. Hanania, Edward Kerwin, Ian Pavord, Huib Kerstjens, Steven Pascoe, Guy Peachey, Andrew Fowler, Zelig Bailes, Dawn Edwards, Neal Sule, Neil Barnes, Frances Gardiner, Laurie A. Lee

Introduction: Little evidence exists that doubling inhaled corticosteroid (ICS) dose improves clinical outcomes. We evaluated this in inadequately controlled asthma patients receiving ICS/long-acting β_2 -agonist (LABA) therapy.

Methods: Phase IIIA, randomized, double-blind, 24–52 week, parallel-group study in adults with asthma with pre-bronchodilator FEV₁ <85% and Asthma Control Questionnaire (ACQ-6) score \geq 1.5, receiving ICS/LABA with daily >250 mcg fluticasone propionate/equivalent. Following 3-week run-in and 2-week stabilization on open-label low-medium dose ICS/LABA, patients were randomized to once-daily FF/VI (100/25, 200/25 mcg) or FF/umeclidinium/VI (100/31.25/25, 100/62.5/25, 200/31.25/25, 200/62.5/25 mcg) via Ellipta inhaler. Endpoints for FF/VI 200/25 mcg versus 100/25 mcg are reported here: mean change from baseline in trough FEV₁ at Week 24 (primary), annualized moderate/severe asthma exacerbation rates, proportion of ACQ-7 and St George's Respiratory Questionnaire (SGRQ) responders (Week 24).

Results: During run-in and stabilization, ICS/LABA therapy provided clinically meaningful improvements from baseline in mean [SD] trough FEV₁ (287 [356] mL) and ACQ-6 score (0.632 [0.762]) in the intent-to-treat population (n=2436). Post randomization, FF/VI 200/25 mcg improved mean trough FEV₁ versus FF/VI 100/25 mcg by 51 mL (95% CI: 8, 95) and reduced exacerbation rate versus 100/25 mcg (rate ratio [95% CI]: 0.65 [0.50, 0.85]). Responder rates for FF/VI 200/25 mcg versus 100/25 mcg were 58% versus 52% for ACQ-7 (OR 1.34; 95% CI: 1.00, 1.79), and 68% versus 64% for SGRQ (OR 1.21; 95% CI: 0.89, 1.63). There was no increase in adverse events for FF/VI 200/25 mcg versus 100/25 mcg.

Conclusions: Doubling FF dose in inadequately controlled asthma patients on FF/VI reduces exacerbations by 35% and provides modest improvements in FEV₁ and ACQ-7, demonstrating an ICS dose response on outcomes.

Funding: GSK (study 205715/NCT02924688).

Reprinted from Journal of Allergy and Clinical Immunology, 145(2 Suppl), Hanania N, Kerwin E, Pavord I, Kerstjens H, Pascoe S, Peachey G, Fowler A, Bailes Z, Edwards D, Sule N, Barnes N, Gardiner F, Lee L, Step-up to high dose fluticasone furoate in combination with long-acting bronchodilator in inadequately controlled asthma: the CAPTAIN study, AB24, Copyright 2020, with permission from Elsevier

Asphyxiation in an adolescent patient with HAE: Importance of an HAE management plan

H. Henry Li and John Dang

Introduction:

Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is an autosomal dominant disorder characterized by recurrent, disabling, and potentially life-threatening attacks of nonpruritic edema commonly affecting the face, limbs, extremities, trunk, abdomen and upper airways. Attacks involving the larynx are medical emergencies and immediate treatment with on-demand medication is recommended to help prevent asphyxiation. Children are especially at risk for mortality from laryngeal attacks due to the smaller diameter of the airway. We report on a male adolescent patient with a strong family history of HAE that died from a laryngeal attack in his home that did not have access to readily available on-demand medications.

Case Presentation:

The boy, a 13-year old with over 20 diagnosed family members with HAE, initially had an episode of hand swelling at age 9. He was later confirmed to have HAE type I. However, he was never seen by an HAE specialist. His mother has HAE and was managed by a primary care physician. The family reported the patient remained asymptomatic until age 13 when he started to experience hand swelling again. One evening he complained to his father that he had trouble swallowing and breathing. The boy called his grandmother who has HAE and she told him to take an over the counter antihistamine and go back to bed. Later in the evening he told his father his breathing had become more difficult and it was now very hard to breathe. His father called 911 but by the time EMS arrived he was found dead in his room. The cause of death was determined to be a laryngeal attack resulting in asphyxiation.

Discussion/Conclusions:

An individualized HAE management plan involving an expert physician and HAE patients should be developed which includes access to emergency on-demand medications in order to help prevent potentially fatal laryngeal attacks.

Funding: CSL Behring

Durability of symptom control with long-term prophylactic therapy with subcutaneous c1-inhibitor in patients with hereditary angioedema

Timothy Craig, Henrike Feuersenger, Ingo Pragst

Introduction:

Hereditary angioedema (HAE) due to C1-inhibitor (C1-INH) deficiency is characterized by recurrent nonpruritic edema that commonly affects the face, limbs, and trunk, and submucosal tissues. Attacks may be disfiguring, painful, and, in the case of upper airway involvement, potentially fatal. The goal of prophylactic therapy is to decrease the number and severity of angioedema attacks. Despite prophylaxis, patients may experience breakthrough attacks. We evaluated the durability of symptom control and patterns of rescue medication use with subcutaneous C1-INH inhibitor (C1-INH [SC]) in HAE patients treated in an open-label extension (OLE) of the phase III COMPACT trial.

Methods:

The OLE of the COMPACT trial was a multicenter, international, randomized, parallel-arm study that evaluated patients aged ≥ 6 years with ≥ 4 attacks over 2 consecutive months before enrollment. The trial included C1-INH (SC)-naïve patients and rollover patients from COMPACT. Patients were randomized to receive C1-INH (SC) 40 IU/kg or 60 IU/kg twice weekly for 52 weeks (up to 140 weeks for US patients).

Results:

Of the 126 patients treated in the OLE, 63 patients received the FDA approved dose of 60 IU/kg and were included in this analysis. Of these patients, 92% were classified as responders, with $\geq 50\%$ reduction in attacks vs pre-study; 31 (49.2%) of patients experienced an attack rate < 1 attack per year. Thirty-nine patients (61.9%) used no on-demand medication; 66.7% used on-demand medication less than once per year (mean [SD]: 3.8 [9.6] uses/year; median: 0.0 uses/year). The median time until patients experienced their first attack was 224 days. Among patients with > 2 years of C1-INH (SC) 60 IU/kg exposure, 87% did not use any rescue medication during months 25 to 30.

Conclusions:

C1-INH (SC) was effective as long-term prophylaxis with a median annualized attack rate of 1.0 with almost two-thirds of patients requiring no use of on-demand medication.

Funding: CSL Behring

Safety profile of high IgPro20 infusion parameters in patients with primary immunodeficiency (PID): Results from The Forced Upward Titration HILO study

Mikhail A. Rojavin, Connie Hsu, John Anderson, Vincent R. Bonagura, Juthaporn Cowan, Patricia L. Lugar, Paul J. Maglione, S. Shahzad Mustafa, Niraj C. Patel, John M. Routes, Panida Sriaroon, Donald C. Vinh, Michaela Praus, Jutta Hofmann

Introduction: The Hizentra® Label Optimization (HILO) study (NCT03033745) assessed safety and tolerability of increasing infusion rates and volumes of subcutaneous immunoglobulin (SCIg) in patients with primary immunodeficiency (PID).

Methods: In this open-label nonrandomized phase 4 study, patients receiving IgPro20 (Hizentra®, CSL Behring) were assigned to: Pump-assisted Volume Cohort (n=15; 25–50 mL/injection site, weekly); Pump-assisted Flow Rate Cohort (n=18; 25–100 mL/h/injection site, weekly); or Manual Push Flow Rate Cohort (n=16; 30–120 mL/h/injection site; 2–7 infusions/week). Assignments were based on prior experience with pump-assisted infusions at the highest approved IgPro20 parameters or frequent manual push infusions (~25 mL/h). Treatment-emergent adverse events (TEAEs) were evaluated.

Results: The rate of TEAEs per infusion was low across all cohorts: 0.145, 0.228, and 0.085 in the Pump-Assisted Volume Cohort, the Pump-Assisted Flow Rate Cohort, and the Manual Push Flow Rate Cohort, respectively. There were no clinically meaningful differences in TEAE frequency, type, intensity, or duration among cohorts, and rates of TEAEs per infusion did not increase with increasing infusion parameters. Most TEAEs were mild or moderate infusion site reactions (ISRs). Causally-related ISRs occurred in 4 patients (26.7%) in the Pump-Assisted Volume Cohort (0.079/infusion); 1 patient discontinued due to mild injection site pain. In the Pump-Assisted Flow Rate Cohort, 8 patients (44.4%) had related ISRs (0.131/infusion); 1 patient (5.6%) reported 2 severe causally-related ISRs, but none discontinued. In the Manual Push Flow Rate Cohort, 6 patients (37.5%) had causally-related ISRs (0.043/infusion); 1 patient (6.3%) had a severe, unrelated serious TEAE (suicide attempt) leading to discontinuation.

Conclusions: High infusion parameters for pump-assisted and manual push subcutaneous IgPro20 infusions had an acceptable safety profile. No new safety signals were reported, and no trends indicated an increase in TEAE intensity or frequency with increasing flow rate or volume.

Funding: CSL Behring

The HILO Study: High volumes and flow rates of subcutaneous IgPro20 pump-assisted infusions in patients with primary immunodeficiency

John Anderson, Vincent R. Bonagura, Juthaporn Cowan, Connie Hsu, S. Shahzad Mustafa, Niraj C. Patel, John M. Routes, Panida Sriaroon, Donald C. Vinh, Jutta Hofmann, Michaela Praus, Mikhail A. Rojavin

Introduction: The Hizentra® Label Optimization (HILO) study evaluated the safety and tolerability of high infusion parameters of subcutaneous immunoglobulin, IgPro20 (Hizentra®, CSL Behring), administration in patients with primary immunodeficiency (PID). Here we report the results in patients who received pump-assisted IgPro20 administration.

Methods: HILO was the first multicenter, open-label, parallel-arm, nonrandomized study (NCT03033745), in which patients received weekly IgPro20 infusions at a constant dose using forced upward titration design. Eligible patients were experienced with pump-assisted infusions at the approved highest IgPro20 infusion parameters. Responder rates (percentage of patients who successfully completed $\geq 75\%$ of planned infusions) in the Pump-assisted Volume Cohort (n=15; 25–50 mL per injection site) and in the Pump-assisted Flow Rate Cohort (n=18; 25–100 mL/h per injection site), adherence rates, and serum immunoglobulin G (IgG) trough levels were evaluated.

Results: Responder rates were 86.7% (25 mL), 73.3% (40 and 50 mL) and 77.8% (25 and 50 mL/h), 66.7% (75 mL/h), 61.1% (100 mL/h) in the Volume and Flow Rate Cohorts, respectively. Dose and volume adherence rates were $\geq 90\%$ in all patients of the Volume Cohort, and in 83.3% of patients in the Flow Rate Cohort ($< 90\%$ in 3 patients). Mean (standard deviation) IgG trough levels (g/L) were similar between Day 1 and study end in both the Volume (10.19 [2.35] vs 10.96 [2.42]) and Flow Rate (10.40 [2.06] vs 10.62 [1.87]) Cohorts.

Conclusions: Despite decreasing responder rates, pump-assisted IgPro20 infusions are feasible and tolerable at high infusion parameters in most patients, allowing shorter infusion times and thereby improved administration convenience. Increasing infusion parameters had no negative impact on the tolerability of IgPro20.

Funding: CSL Behring

Feasibility of subcutaneous IgPro20 administration via manual push at high flow rates in patients with primary immunodeficiency: Findings of the HILO Study

Juthaporn Cowan, Vincent R. Bonagura, Patricia L. Lugar, Paul J. Maglione, Niraj C. Patel, Donald C. Vinh, Michaela Praus, Jutta Hoffman, Mikhail A. Rojavin

Introduction: The safety and tolerability of high infusion parameters in subcutaneous immunoglobulin (SCIg) administration has not been previously studied. The Hizentra® Label Optimization (HILO) study evaluated the feasibility of high infusion flow rates and volumes of pump-assisted and manual push administration of subcutaneous IgPro20 (Hizentra®, CSL Behring, United States) in patients with primary immunodeficiency (PID).

Methods: The HILO study was a multicenter, open-label, parallel-arm, non-randomized study, which evaluated high infusion parameters using a forced upward titration design (NCT03033745). Here, we report the results of the Manual Push Flow Rate Cohort (n=16) which included patients experienced with frequent IgPro20 infusions (2–7 infusions/week) at the highest flow rate approved for pump-assisted infusions (~25 mL/h or ~0.5mL/min). High infusion flow rates including 0.5, 1, and 2 mL/min were evaluated, while weekly IgPro20 dose, dosing frequency, and infusion volume remained constant during the study period (12 weeks). Responder rates (% of patients completing at least 60% of infusions at each flow rate and completing the full dose per scheduled infusion), compliance rates, and serum immunoglobulin G (IgG) trough levels were assessed.

Results: Responder rates were 100%, 100% and 87.5% at 0.5 mL/min, 1 mL/min, and 2 mL/min, respectively, with 98.5–100% of infusions completed per planned schedule. Dose compliance rate was ≥90% in 15/16 patients. Mean (standard deviation) IgG trough levels were similar between Day 1 (9.36 [2.53] g/L) and end of study (9.58 [2.12] g/L).

Conclusions: Manual push IgPro20 infusions at high flow rates (up to 2 mL/min/site) are feasible in most patients with PID and increasing the flow rate did not impact IgPro20 tolerability. Higher manual push flow rates may allow patients to individualize their SCIg therapy by reducing infusion time.

Funding: CSL Behring

Exhalation delivery system with fluticasone treatment in subjects not controlled with conventional intranasal steroids

Ellen Sher, David Elkayam, Harry Sacks, John Messina

Introduction: The exhalation delivery system with Fluticasone (EDS-FLU) delivers steroid more posteriorly and superiorly within the nasal cavity than conventional nasal sprays. Placebo-controlled efficacy studies with EDS-FLU in nasal polyps (NAVIGATE I/II) included subjects with moderate/severe congestion despite using conventional nasal steroids. This is a new analysis of change in disease activity in the subgroup of patients who reported using an INS at the time of screening.

Methods: Patients in NAVIGATE I & II were required to have bilateral polyposis and at least moderate congestion over the 2 weeks prior to entry. Subjects who were using INS within 30 days of the screening visit were included in this pooled post-hoc analysis. Change in co-primary endpoints (congestion/obstruction, polyp grade reduction) and in SNOT-22 was assessed.

Results: Of 482 patients, 218 (45.2%) had used an INS within 30 days at screening; ≈3 years average duration with ≈80% using >60-days. Following EDS-FLU treatment, significant improvements were observed: congestion at week 4 (EDS-PBO: -0.24; EDS-FLU 186µg; -0.6 [P<0.001]; EDS-FLU 372µg: -0.74 [P<0.001]), polyp grade at week 16 (EDS-PBO: -0.43; EDS-FLU 186µg: -1.15 [P<0.001]; EDS-FLU 372µg: -1.38 [P<0.001]), and SNOT-22 at week 16 (EDS-PBO: -8.3; EDS-FLU 186µg: -21.0 [P<0.001]; EDS-FLU 372µg: -21.1 [P<0.001]). Similar results were observed in patients not on an INS at study qualification and for the total population.

Conclusions: This analysis demonstrates that EDS-FLU provides significant reduction in disease severity in patients with nasal polyps and moderate/severe congestion who have an unsatisfactory response to standard steroid nasal sprays.

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Twice-daily administration of exhalation delivery system with fluticasone and patient satisfaction

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Introduction: International guidelines recommend intranasal corticosteroids (INS) to improve symptoms and patient-reported outcomes in chronic rhinosinusitis with and without nasal polyps (CRSwNP/CRSsNP). Exhalation delivery system with fluticasone (EDS-FLU) delivers INS high and deep in the nasal passages (ie, ostiomeatal complex). Though the recommended dosage of most conventional INS is twice daily (BID) and evidence suggests that topical INS BID may offer better efficacy than once daily (QD) for patients with CRSwNP, INS may be used (or are prescribed) QD or less. A survey was conducted regarding the use of EDS-FLU to examine the correlation between QD, BID, or not-daily use with patient satisfaction.

Methods: Patients prescribed EDS-FLU were surveyed to assess how often they used EDS-FLU (BID, QD, not daily) and how satisfied they were with EDS-FLU. Patients rated their satisfaction on a 5-point Likert scale, with “satisfaction” defined as 4 or 5.

Results: Of 224 patients identified as having received an EDS-FLU prescription, 73 with CRSwNP and 48 CRSsNP consented to respond. Of the patients responding (N = 121), 67 reported using EDS-FLU BID, 39 reported QD, and 15 reported infrequent use (less than daily). More patients using EDS-FLU BID indicated satisfaction with EDS-FLU compared with patients using EDS-FLU QD (76% vs 59%). Only 40% of patients who reported infrequent use of EDS-FLU were satisfied. The number of patients using EDS-FLU BID who reported satisfaction was similar among patients with CRSwNP and CRSsNP ([77%] and [74%], respectively). Also, fewer patients with CRSwNP or CRSsNP expressed satisfaction when they infrequently used EDS-FLU ([50%], and [36%], respectively).

Conclusions: More patients with CRS who used EDS-FLU twice daily reported satisfaction compared with patients using EDS-FLU once daily or less. This real-world evidence is consistent with prior studies of INS showing that twice daily administration provides more reliable efficacy compared with once daily.

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Efficacy and safety trends with continuous long-term use of crisaborole ointment, 2%, in patients with mild-to-moderate atopic dermatitis

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Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin disease that often requires long-term treatment. Crisaborole significantly improved global signs and symptoms of AD in phase 3 studies. We report the efficacy and safety of continuous, long-term use of crisaborole in patients aged ≥2 years with mild-to-moderate AD based on a post hoc analysis of a 48-week, open-label, phase 3 extension study.

Methods: Patients were evaluated every 28 days. Patients with ISGA ≥2 received crisaborole for a 28-day cycle (on treatment). Patients with Investigator’s Static Global Assessment (ISGA) 0 (clear)/1 (almost clear) did not receive crisaborole for the next 28-day cycle (off treatment). Patients were stratified by number of initial consecutive 28-day cycles of crisaborole received during the 48-week period.

Results: Included in exclusive cohorts were 418 patients (1 on-treatment cycle [28 days], n=133; 2 consecutive on-treatment cycles [56 days], n=106; 3 consecutive on-treatment cycles [84 days], n=106; 4 consecutive on-treatment cycles [112 days], n=73). In all groups, <6% of patients discontinued treatment during initial consecutive on-treatment cycles. After 1-4 initial consecutive on-treatment cycles, 77.6% (97/125), 76.3% (74/97), 59.4% (63/106), and 43.1% (31/72) of patients achieved ISGA 0/1, respectively. Of these patients, 49.5%, 37.8%, 44.4%, and 45.2% maintained ISGA 0/1 at the end of the next 28-day cycle off treatment. After being off treatment, treatment was restarted in 79.4%, 81.1%, 87.3%, and 77.4% of the patients who previously achieved ISGA 0/1 at the end of the initial treatment period. Incidences of treatment-related adverse events (AEs) were 4.5%, 4.7%, 3.8%, and 1.4% for patients receiving 1-4 consecutive on-treatment cycles. One patient discontinued because of AEs.

Conclusion: Continuous long-term treatment with crisaborole beyond 28 days may be necessary to maintain control of AD symptoms in some patients with mild-to-moderate AD. Continuous long-term crisaborole use was well tolerated.

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Efficacy and safety of crisaborole in patients ≥ 3 months of age with mild-to-moderate atopic dermatitis (AD)

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Introduction: Crisaborole ointment, 2%, is an anti-inflammatory nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD. We report efficacy and safety of crisaborole across age groups in the phase 3 studies CrisADe CORE 1 (AD-301; NCT02118766) and CORE 2 (AD-302; NCT02118792) and the phase 4 study CrisADe CARE 1 (NCT03356977).

Methods: Patients aged 3 to < 24 months (CARE 1) or ≥ 2 years (CORE 1/CORE 2) with mild-to-moderate AD received twice-daily crisaborole (or vehicle in CORE 1/CORE 2) for 28 days. Safety was the primary endpoint in CARE 1. ISGA success (clear [0] or almost clear [1] with a ≥ 2 -grade improvement from baseline) at day 29 was an endpoint in CARE 1 (exploratory) and CORE 1/CORE 2 (primary).

Results: CARE 1 included 137 infants, all treated with crisaborole (mean age, 13.6 months). In CORE 1/CORE 2, 1016 patients were treated with crisaborole (ages 2-6 years, n=335; 7-11 years, n=292; 12-17 years, n=247; ≥ 18 years, n=142). Rates of treatment-related application site pain (3.6%) and application site discomfort (2.9%) reported in CARE 1 were consistent with rates of application site pain reported for crisaborole-treated patients in CORE 1/CORE 2 (4.4% overall; 2-6 years, 3.6%; 7-11 years, 5.5%; 12-17 years, 4.1%; ≥ 18 years, 5.0%). In CARE 1, 30.2% of patients achieved ISGA success at day 29, consistent with that observed for crisaborole-treated patients in CORE 1/CORE 2 (32.1% overall; 2-6 years, 30.5%; 7-11 years, 36.6%; 12-17 years, 30.3%; ≥ 18 years, 29.7%). Rates of ISGA clear/almost clear at day 29 were 47.3% in CARE 1 and 50.1% in crisaborole-treated patients in CORE 1/CORE 2 (2-6 years, 47.3%; 7-11 years, 54.7%; 12-17 years, 50.0%; ≥ 18 years, 47.8%).

Conclusions: Based on these studies, crisaborole was well tolerated and effective in adults, adolescents, children, and infants ≥ 3 months of age with mild-to-moderate AD.

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Reduction in use of On-Demand Medication with Prophylactic Berotralstat Treatment

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Introduction: Hereditary angioedema (HAE) is rare disorder characterized by subcutaneous and submucosal swelling mediated by bradykinin. Attacks are unpredictable and acute treatment is often required. Berotralstat (BCX7353) is an oral, once daily, inhibitor of plasma kallikrein in development for prophylaxis of HAE. This exploratory analysis evaluated the use of acute, on-demand medications during treatment with berotralstat.

Methods: APeX-2 is a double-blind, placebo-controlled study in subjects with HAE Type 1 or 2. Subjects were randomized 1:1:1 to berotralstat 110mg;berotralstat 150mg;placebo daily for 24 weeks. Subjects were to treat HAE attacks according to their usual treatment plan. Retreatment was defined as use of > 1 dose of SOC on-demand medication to treat an attack.

Results: Overall, the rate of attacks requiring treatment was significantly lower with berotralstat 150 mg compared to placebo (150mg, -49.2%, nominal $p < 0.001$). The rates of on-demand medication use per 28 days for investigator-confirmed attacks were less for berotralstat 150 mg (1.29) compared with placebo (2.79) resulting in 53.6% rate reduction (nominal $p < 0.001$). The reduction in rate of on-demand medication use equates to approximately 1.5 fewer doses of on-demand medication per month for the 150-mg dose group compared with placebo.

Conclusions: Patients receiving berotralstat had fewer attacks, treated fewer attacks, and used less on-demand medication compared with placebo, suggesting reduced attack severity on berotralstat.

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