425 Molecular diagnosis of hereditary angioedema patients using a 77 gene NGS panel

Keith Wetherby[1], Shaobin Hou[1], Lili Wan[1], Emily Faulkner[1], Priyanka Kundu[1], Huamin Li, MD PhD FAAAAI[2]; [1]Virant Diagnostics, [2]Institute for Asthma and Allergy.

RATIONALE: Hereditary Angioedema (HAE) is a rare autosomal dominant genetic disease frequently caused by mutations in the C1 inhibitor gene SERPING1, resulting in dysregulated kallikrein–kinin system (KKS) and overproduction of bradykinin. Despite a constellation of pathogenic mutations identified in SERPING1 and 5 others genes in the KKS pathway, genetic diagnosis of some patients with unknown HAE causing mutations but clear HAE clinical presentations are elusive. Genetic modifiers that may contribute to disease severity remains to be investigated. We carried out a pilot study to provide molecular diagnosis for HAE patients using a custom designed 77 gene Next Generation Sequencing (NGS) panel.

METHODS: Genomic DNA is extracted from peripheral blood and screened for mutations using a custom 77 gene NGS panel. Exon level duplications/deletions were identified using multiplex ligation-dependent probe amplification. The impact of variants was evaluated using commercial and publicly available computational tools.

RESULTS: Among the 81 samples sequenced [52 HAE, 26 non-HAE, 3 healthy controls], we found pathogenic SERPING1 mutations in 50 (96%) of the 52 HAE samples, including a gross heterozygous deletion of exons 1-6. Additional variants of unknown significance meeting computational and segregation analysis criteria were identified as potentially impacting genotype-phenotype in two large families. Additional variants identified in our NGS panel suggest possible HAE disease modifying genes that corelate with phenotypic severity.

CONCLUSIONS: We designed and validated a comprehensive HAE molecular diagnosis workflow that has the potential to improve clinical diagnosis and assist in treatment option selections.

426 Berotralstat Improved Quality of Life through 96 Weeks Across Multiple Subgroups of Patients with Hereditary Angioedema

Daniel Soteres, MD FAAAAI[1], William Lumry, MD FAAAAI[2], Markus Magerl, MD PhD[3], Remi Gagnon, MD, MSc[4], Bhavisha Desai, PharmD[5], Dianne Tomita, MPH[5], Douglas Johnston[6], Marcus Maurer, MD[7]; [1]Asthma and Allergy Associates, P. C., [2]Allergy and Asthma Specialists, [3]Universitatsmedizin Berlin, [4]Clinique Spécialisée en Allergie de la Capitale, [5]BioCryst Pharmaceuticals Inc., [6]BioCryst Pharmaceuticals, Inc., [7]Charite-Universitatsmedizin Berlin.

RATIONALE: Berotralstat is a first-line, once-daily (QD) oral prophylaxis for hereditary angioedema (HAE) shown to reduce the burden of disease and treatment. We present patient-reported quality of life (QoL) in patients who received berotralstat in APeX-2 (NCT03485911).

METHODS: QoL was assessed using the validated Angioedema-QoL questionnaire (AE-QoL), and stratified by baseline age, sex, baseline attack rate, prior prophylaxis, and by incidence of gastrointestinal adverse events (GI AEs) during berotralstat therapy. Decreasing scores indicated QoL improvement. The minimal clinically important difference (MCID) is a 6-point reduction in total score.

RESULTS: In patients who received berotralstat 150 mg (N=40) mean (SEM) improvements from baseline to Week 96 in total AE-QoL score exceeded the MCID value from Week 4 and were sustained through 96 weeks when stratified by age (Week 96, <35 years, -23.6 [7.9]; 35–50 years, -21.4 [2.5]; >50 years, -24.5 [6.9]), sex (female, -23.9 [4.6]; male, -21.7 [6.0]), baseline attack rate (<2/month, -24.7 [8.9]; ≥2/month:,-22.4 [3.9]), and prior prophylaxis (prior androgens, -19.4 [5.3]; prior C1 inhibitor, -21.6 [3.8]). Mean (SEM) total AE-QoL score improved from baseline to Week 96 regardless of the presence (n=11; -18.2 [4.9]) or absence (n=8; -29.5 [4.4]) of GI AEs during the first 24 weeks on berotralstat. Improvements were reflected across all QoL domains (functioning, fatigue/mood, fear/shame, nutrition) through 96 weeks irrespective of stratification. Across most subgroups, the largest improvement occurred in the functioning domain.

CONCLUSIONS: Long-term prophylaxis with berotralstat led to sustained and clinically meaningful improvements in patient-reported QoL across multiple subgroups, suggesting sustained reductions in disease and treatment burden.

427 Health-Related Quality of Life (HRQoL) in Pediatric Patients with Hereditary Angioedema (HAE) Receiving Lanadelumab: Exploratory Results From the SPRING Study

Maureen Watt, Msc[1], Marcus Maurer, MD[2], William Lumry, MD FAAAAI[3], H. Henry Li[4], Emel Aygören-Pürsün, MD[5], Paula Busse, MD FAAAAI[6], Joshua Jacobs, MD[7], Christina Nurse, PhD[1], Ming Yu[1], Dorothy Romanus[1], Giovanna Devercelli[1]; [1]Takeda Development Center Americas, Inc., Lexington, MA, USA, [2]Charité – Universitätsmedizin Berlin, Berlin, Germany; and Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany, [3]Allergy and Asthma Research Associates, Dallas, TX, USA, [4]Institute for Asthma and Allergy, Chevy Chase, MD, USA, [5]Angioedema Centre, University Hospital Frankfurt, Goethe University, Frankfurt, Germany, [6]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [7]Allergy and Asthma Clinical Research, Walnut Creek, CA, USA.

RATIONALE: An exploratory objective of the Phase III, open-label, multicenter SPRING Study (NCT04070326) was to evaluate the effect of lanadelumab on HRQoL in patients with HAE aged 2–<12 years.

METHODS: Patients aged 2–<6 and 6–<12 years received lanadelumab 150 mg Q4W and Q2W, respectively, for 52 weeks. HRQoL was evaluated at baseline and end-of-study (EOS) using proxy-rated Pediatric Quality of Life Inventory (PedsQL) and the EuroQoL-5-Dimension Youth version (EQ-5D-Y). Parent/caregiver burden was evaluated using PedsQL Family Impact Module (PedsQL-FIM). Results from a post-hoc analysis are reported.

RESULTS: PedsQL total score increased (improved HRQoL) from baseline to EOS: mean(SEM) +30.63(9.38) in 2 toddlers (2–4 years), +30.00(8.30) in 5 young children (5–7 years), +14.31(3.38) in 12 children (8–12 years). HRQoL improvement from baseline to EOS achieved minimal clinically important difference (4.5 points in PedsQL total score) in 100% toddlers, 80% young children, 69.2% children. The overall mean(min, max) EQ-5D-Y visual analogue scale score was 93.8(71, 100) at baseline and 97.5(85, 100) at EOS. In each EQ-5D-Y dimension, ≥75% patients reported no problems at baseline, EOS, and throughout the study. The total PedsQL-FIM score increased (better functioning, less negative impact) from baseline to EOS in safety population: mean(SEM) +18.85(3.37); improvement was similar for lanadelumab 150 mg Q4W (+16.67[2.50]) and Q2W (+19.24[3.96]) groups. Improvements were reported for all PedsQL and PedsQL-FIM dimensions.

CONCLUSIONS: Lanadelumab 150 mg Q4W (patients aged 2–<6) and Q2W (patients aged 6–<12) was associated with HRQoL improvement and reduced parent/caregiver burden, supporting lanadelumab use in this population.