Distinguished Industry Oral Abstracts

Adverse Drug Reactions, Insect Reactions, Anaphylaxis

D001

PHARMACOKINETICS STUDY OF EPINEPHRINE SUBLINGUAL FILM: RESULTS FROM THE FORMULATION AND DOSAGE SELECTION

M. Freedman[1], J. Oppenheimer[2], S. Wargacki[3], G. Slatko[3],
1. Toronto, ON, Canada; 2. Cedar Knolls, NJ; 3. Warren, NJ.

Introduction: We have previously published the results from a first in human study that identified a prototype producing pharmacokinetics (PK) and pharmacodynamics (PD) of a sublingual film using a novel prodrug epinephrine (DESF). Three commercially viable formulations, across two dosage strengths each, are explored to establish a bridge to the lead formulation identified in a previous first in human study.
Methods: EPIPHAST is a randomized, open-label, three-part adaptive design, crossover study in healthy adult subjects comparing the PK and PD of DESF. In its Phase 1, multiple oral film formulations and dosage strengths of DESF were evaluated to identify an intended final formulation. Sixteen healthy volunteers were selected for each formulation and dosage, or a 0.5 mg IM injection of epinephrine for comparison.
Results: Seven different configurations were examined, and PK parameters were measured. The two best formulations of DESF (Formulation 5: 10 mg and 12 mg) rapidly reached clinically meaningful blood concentrations, with a median Tmax of 15 minutes and 22.5 minutes, respectively. Mean Cmax values were 285pg/mL and 268pg/mL for the two configurations, respectively. Formulation 5 at 12 mg produced results most comparable to both the first in human study as well as those reported for IM injections of epinephrine. The adverse event profiles and tolerability were similar across all formulations and dosage strengths.
Conclusion: The findings show that DESF formulations can deliver sufficient blood concentrations of epinephrine sooner than that observed with the higher dose of IM epinephrine injection in line with existing epinephrine autoinjectors and without concerns for safety or tolerability.

Angioedema/Urticaria

D005

PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA MAY BENEFIT FROM LONGER TREATMENT OR UPDOSING WITH OMALIZUMAB

G. Mosnaim[1], T. Casale[2], M. Holden[3], B. Trzaskoma[4], J. Bernstein[5],
1. Glenview, IL; 2. Tampa, FL; 3. San Francisco, CA; 4. South San Francisco, CA; 5. Cincinnati, OH.

Introduction: Chronic spontaneous urticaria (CSU/CIU) is a debilitating skin disorder. The EAACI/GA2LEN/EDF/WAO guidelines recommend omalizumab as second-line treatment (after H1-antihistamines) for 6 months before switching to cyclosporin-A. However, in clinical practice the decision to discontinue omalizumab is often made before the recommended 6 months, and, although characteristics including lower IgE levels and higher BMI may be associated with poor response, these same patients may benefit from longer treatment/up-dosing.
Methods: Post hoc analysis of the XTEND-CIU (NCT02392624) randomized study with patients ≥12 years with symptomatic CIU/CSU (UAS7≥16) despite H1-antihistamines (24-week open-label period [omalizumab 300mg SCQ4W] before randomization 3:2 to 24-week omalizumab:placebo). For the open-label period, early responders were defined as UAS7≤6 at Week 12 and late responders as UAS7≤6 at Week 24 but not at Week 12. Patients were categorized by baseline IgE level quartiles and BMI ≥30 or <30.
Results: Over half 58.82% (120/204) of patients were early responders and 15.69% (32/204) were late responders (14/32 [43.75%] had autoantibodies at screening). For IgE, 36.67% of late responders and 22.89% of patients who were not late responders (early responders plus others) fell into the first quartile of baseline levels (<32.5 IU/mL). For BMI, 53.13% of late responders and 43.02% of patients who were not late responders had baseline BMI ≥30. Overall safety in Casale JACIP 2019;7;2487-90.
Conclusions: Patients with CSU with a poor response following 12 weeks of omalizumab may benefit from longer treatment/up-dosing if they had low IgE and/or high BMI at treatment initiation, which may assist treatment decision-making.

D006

RAPID AND SUSTAINED REDUCTIONS IN HEREDITARY ANGIOEDEMA ATTACK RATES WITH LONG-TERM BEROTRALSTAT: REAL-WORLD OUTCOMES

W. Lumry[1], B. Desai[2], A. Tilley[2], D. Johnston[2], S. Wasilewski[3], T. Craig[4],
1. Dallas, TX; 2. Durham, NC; 3. Earth City, MO; 4. Hershey, PA.

Introduction: Berotralstat, an oral once-daily prophylactic treatment for hereditary angioedema (HAE), has demonstrated sustained reduction in HAE attack rates and improvements in patient-reported quality of life in clinical trials. Here we present the preliminary efficacy data of patients in the United States receiving berotralstat in the real-world clinical setting.
Methods: This analysis is data collected through the sole-source pharmacy and included patients with confirmed HAE Type I/II based on laboratory tests and actively received berotralstat 110 or 150mg from 12/16/2020 to 5/20/22 for >270 days. Baseline attack rates were reported for the 90 days prior to berotralstat initiation. While on therapy, median attacks/month (25^{th},75^{th} percentile) were calculated over each 90-day period by averaging each patient's monthly reported attack rate (1 month=∼28 days). Some patients did not report attack rates at each refill.
Results: In the patients who actively received berotralstat for >270 days (n=128) the median baseline attack rate was 1.7 attacks/-month. A rapid reduction in median monthly attack rates was observed after starting berotralstat. During the first 90 days on therapy (days 1-90) the median monthly attack rate decreased to 0.3 (0,1.50) attacks/month; 0.5 (0,1.00) attacks/month from days 91-180; 0.3 (0,1.25) attacks/month from days 181-270; and 0.3 (0,1.25) attacks/month from days 271-360. The most common adverse events reported were consistent with clinical trials.
Conclusions: This data shows that berotralstat provided a rapid and sustained reduction in HAE attack rates within the first months of starting therapy making oral berotralstat an effective treatment option for patients with HAE.

D007

IN VIVO CRISPR/CAS9 EDITING OF KLKB1 IN PATIENTS WITH HEREDITARY ANGIOEDEMA: A FIRST-IN-HUMAN STUDY

H. Longhurst[1], L. Fijen[2], K. Lindsay[3], J. Butler[4], A. Golden[4], D. Maag[4], Y. Xu[4], D. Cohn[2], *1. Auckland, New Zealand; 2. Amsterdam, Netherlands; 3. Amsterdam, Noord-Holland, Netherlands; 4. Cambridge, MA.*

Introduction: Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent, debilitating and potentially fatal swelling attacks. Prophylactic treatments targeting kallikrein, a

protease encoded by the *KLKB1* gene, significantly reduce the frequency of attacks. NTLA-2002 is an investigational CRISPR/Cas9-based therapy targeting *KLKB1* in hepatocytes, with the goal of achieving life-long control of HAE attacks after a single administration.
Methods: NCT05120830 is a first-in-human phase 1/2 study of NTLA-2002 in patients with HAE. The phase 1 is a single-ascending dose design with the primary objective of evaluating safety and identifying up to two doses to advance to the randomized phase 2 for further evaluation of efficacy and safety.
Results: Cohort 1 (25 mg; n = 3) completed the 16-week primary observation period. No DLTs or clinically significant laboratory abnormalities were observed. TEAEs were non-serious and spontaneously resolving, with the most common being infusion-related reactions (n = 2; CTCAE G1). All subjects demonstrated clinically significant, durable reduction in plasma kallikrein levels (mean 62 ± 27% at week 16) and HAE attack frequency from baseline, with 2 subjects remaining attack-free since infusion. Three subjects have been treated in Cohort 2 (75 mg). Follow-up is ongoing for all subjects in both cohorts.
Conclusion: A single 25 mg dose of NTLA-2002 has been well-tolerated to date, meeting pre-specified criteria for advancement to phase 2 with reduction in plasma kallikrein levels and HAE attack rate maintained throughout the 16-week period following infusion. Safety, pharmacodynamic and HAE attack rate data for both cohorts will be presented.

D008

REMIBRUTINIB IMPROVES CHRONIC SPONTANEOUS URTICARIA IN PATIENTS IRRESPECTIVE OF CU-INDEX: RESULTS FROM PHASE 2B STUDY

W. Carr[1], K. Sitz[2], V. Jain[3], A. Giménez-Arnau[4], K. Lheritier[5], I. Nikolaev[5], S. Haemmerle[5], M. Maurer[6], *1. Mission Viejo, CA; 2. Little Rock, AR; 3. Hamilton, ON, Canada; 4. Barcelona, Spain; 5. Basel, Switzerland; 6. Berlin, Germany.*

Introduction: We explored the effect of remibrutinib (LOU064), a novel oral Bruton's Tyrosine Kinase inhibitor, in chronic spontaneous urticaria (CSU) patients by baseline CU-index.
Methods: In this Phase 2b study (NCT03926611), 311 CSU patients were equally randomized to remibrutinib 10mg once-daily (q.d.)/35mg q.d./100mg q.d./10mg twice-daily (b.i.d.)/25mg b.i.d./100mg b.i.d. or placebo for 12 weeks. Outcomes included changes in weekly Urticaria Activity Score (UAS7) by baseline CU-index-positive (≥10) and -negative (<10) at Weeks 4 and 12, and patients achieving UAS7=0 and UAS7≤6 by CU-index at Week 12.
Results: Of 311 patients, 34.4% were CU-index-positive at baseline. Reductions of mean UAS7 from baseline were higher in CU-index-positive *vs* -negative patients in all remibrutinib arms at Weeks 4 (−18.64 to −30.15 *vs* −12.82 to −19.85) and 12 (−18.91 to −32.50 *vs* −13.56 to −18.29). In the placebo arm, mean UAS7 reduction was higher in CU-index-negative *vs* -positive patients at Weeks 4 (−6.68 *vs* −1.25) and 12 (−9.06 *vs* −5.81). At Week 12, higher proportions of CU-index-positive *vs* -negative patients achieved UAS7=0 (31.6−54.5% *vs* 18.5−34.5%) and UAS7≤6 (50.0−72.7% *vs* 32.1−48.3%) in all remibrutinib arms. In the placebo arm, more CU-index-positive *vs* -negative patients achieved UAS7=0 (21.4% *vs* 11.1%); UAS7≤6 response was similar between subgroups (28.6% *vs* 29.6%) Table 1.
Conclusion: Remibrutinib (all doses) improved UAS7 regardless of baseline CU-index, with greater improvements in CU-index-positive *vs* -negative patients. More patients on remibrutinib achieved UAS7=0 and UAS7≤6 *vs* placebo, irrespective of baseline CU-index. Larger studies are required to confirm the findings from Phase 2b study. UAS7, weekly Urticaria Activity Score.

Table. Change in UAS7 scores from baseline and percentage of patients with UAS7=0 and UAS7≤6, by CU-index status at baseline and treatment group

Outcome	Week	CU-index status at baseline	Remibrutinib (all doses: range)	Placebo
Mean change in UAS7 scores from baseline	4	Positive	−18.64 to −30.15	−1.25
		Negative	−12.82 to −19.85	−6.68
	12	Positive	−18.91 to −32.50	−5.81
		Negative	−13.56 to −18.29	−9.06
Percentage of patients with UAS7=0	12	Positive	31.6 to 54.5	21.4
		Negative	18.5 to 34.5	11.1
Percentage of patients with UAS7≤6	12	Positive	50.0 to 72.7	28.6
		Negative	32.1 to 48.3	29.6

UAS7, weekly Urticaria Activity Score

D009

DUPILUMAB EFFICACY IN PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA BY IGE LEVEL: LIBERTY-CSU CUPID STUDY A

M. Maurer[1], T. Casale[2], S. Saini[3], M. Ben-Shoshan[4], A. Radin[5], B. Akinlade[5], E. Laws[6], L. Mannent[7], *1. Berlin, Germany; 2. Tampa, FL; 3. Baltimore, MD; 4. Montreal, QC, Canada; 5. Tarrytown, NY; 6. Bridgewater, NJ; 7. Chilly-Mazarin, France.*

Introduction: Chronic spontaneous urticaria (CSU) causes recurrent itchy hives and/or angioedema, significantly impacting quality of life. Many patients experience a substantial disease burden despite treatment with licensed and escalated doses of H1 antihistamines.
Methods: In LIBERTY-CSU CUPID Study A (NCT04180488), a randomized, placebo-controlled, 24-week, phase 3 trial, patients (≥6 years) with CSU who remained symptomatic despite H1 antihistamine treatment received add-on dupilumab (n=70) (adults/adolescents ≥60kg: 300mg; adolescents <60kg/children ≥30kg: 200 mg) or matching placebo (n=68) subcutaneously every 2 weeks. Endpoints included change from baseline at Week-24 over 7 days in Itch Severity Score (ISS7), Hives Severity Score (HSS7), and Urticaria Activity Score (UAS7).
Results: Baseline characteristics were balanced; mean ISS7 and UAS7 (dupilumab/placebo) were 16.1/15.7 and 31.9/30.8, respectively. At Week-24, least squares (LS) mean change from baseline in ISS7 (range: 0−21) was −10.2/−6.0 (dupilumab/placebo, respectively) (LS mean difference −4.2; *P*=0.0005) and for UAS7 (range: 0−42) was −20.5/−12.0 (difference −8.5; *P*=0.0003). Baseline median serum total IgE was 101.0IU/mL (overall population). Dupilumab significantly reduced itch (ISS7), hives (HSS7), and urticaria activity (UAS7) at Week-24 regardless of baseline serum total IgE (<100 /≥100IU/mL): ISS7 LS mean difference vs placebo(95% confidence interval) −4.2(−7.86, −0.62)/−4.6(−8.22, −1.04), respectively; HSS7, −4.2 (−7.60, −0.70)/−6.1(−9.95, −2.33); UAS7, −8.2(−15.04, −1.29)/−10.6(−17.72, −3.54). Occurrence of treatment-emergent adverse events (TEAEs) for dupilumab/placebo were 35(50.0%)/40(58.8%); injection-site reactions, 8(11.4%)/9(13.2%); conjunctivitis, 0/1(1.5%); serious TEAEs, 2(2.9%)/5(7.4%).
Conclusion: Dupilumab demonstrated clinically meaningful and statistically significant improvements in patients with H1 antihistamine-resistant CSU regardless of baseline IgE level and was well tolerated.