patients (10 females, 12 males) completed a 1-year treatment. Mean age was 41.8±13.8 years. Twelve patients (54.5%) were ≤ 40 years old (including 6 (27.3%) patients of age ≤30 years). At baseline, mean IGF-1 level was 2.3 (SD 0.7) x ULN (age- and sex-specific) (583.9 ng/mL; SD 182.2) and mean GH concentration was 3.9 (SD 2.8) ng/mL. Both values decreased significantly after 1 year of treatment (P<0.001). Pasireotide LAR dose was increased to 60 mg in 16 (72.7%) patients and decreased to 20 mg in one patient patient due to worsening of diabetes control. The magnitude of mean GH level decrease was the largest within first 6 months (mean change from baseline: -1.75 ng/mL, 95% CI: -2.64, -0.85, P=0.0006). Mean IGF-1 level decreased rapidly within the first 3 months (mean change from baseline: -153.20 ng/mL, 95% CI: -203.20, -103.19, P<0.0001) and remained low during 12-month follow-up. GH level ≤ 1 ng/mL and ≤2.5 ng/mL was achieved by 7 (31.8%) and 17 (77.3%) patients, respectively. Six patients (27.3%) achieved normal IGF-1 level (IGF-1 ≤1 x ULN) (P=0.0275). IGF-1 ≤1.3 x ULN was observed in 11 (50.0%) of patients. Full biochemical control (GH ≤1 ng/mL and IGF-1 ≤1 x ULN) was achieved in 3 (13.6%) patients. Pasireotide LAR treatment resulted in significant increase of mean fasting glucose level: 119.2 (SD 17.3) vs. 107.5 (SD 13.9) mg/dL, P<0.001. The largest change was observed in first 3 months, and it remained stable until month 12. HbA1c level also increased significantly during first 3 months and stayed on similar level during follow-up (mean for month 12: 6.3 (SD 0.6) vs. 5.9 (SD 0.5) % at baseline, P<0.001). **Conclusions:** Pasireotide LAR is an effective treatment in most patients with persistent acromegaly after surgical debulking resistant to first generation SSAs. The largest increase of glycemia occurs during first 3 months of treatment and it remains stable afterwards.

Neuroendocrinology and Pituitary
CLINICAL TRIALS AND STUDY UPDATES IN NEUROENDOCRINOLOGY AND PITUITARY

Safety and Efficacy of Levoketoconazole in the Treatment of Endogenous Cushing's Syndrome (LOGICS): Results From a Double-Blind, Placebo-Controlled, Randomized Withdrawal Study

Sabina Zacharieva, MD[1], Rosario Pivonello, MD[2], Atanaska Elenkova, MD, PhD[1], Miklos Toth, MD, PhD[3], Ilan Shimon, MD[4], Antonio Stigliano, MD, PhD[5], Corin P. Badiu, MD, PhD[6], Thierry Christian Brue, MD, PhD[7], Carmen Emanuela Georgescu, MD, PhD[8], Stylianos Tsagarakis, MD, PhD[9], Fredric J. Cohen, MD[10], Maria Fleseriu, MD[11].

[1]Medical University Sofia, Sofia, Bulgaria, [2]Università Federico II di Napoli, Naples, Italy, [3]Semmelweis University, Budapest, Hungary, [4]Rabin Medical Center and Tel Aviv University, Tel Aviv, Israel, [5]Sant'Andrea Hospital, University of Rome "Sapienza", Rome, Italy, [6]National Institute of Endocrinology CI Parhon, Bucharest, Romania, [7]Aix-Marseille Université and Hôpital de la Conception, Marseille, France, [8]Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania, [9]Evangelismos Hospital, Athens, Greece, [10]Strongbridge Biopharma, Trevose, PA, USA, [11]Oregon Health and Science University, Portland, OR, USA.

Endogenous Cushing's syndrome (CS) is a rare, serious disorder caused by chronic cortisol excess. A phase 3, open-label study (SONICS) demonstrated efficacy and safety of levoketoconazole in adults with CS. LOGICS is a phase 3, double-blind (DB), placebo-controlled, randomized-withdrawal (R-W) study that investigated levoketoconazole in adults with CS via an open-label titration-maintenance (T-M) phase (14-19 weeks) followed by a DB R-W phase (~8 weeks) and a restoration phase (~8 weeks). The primary endpoint is the proportion of patients with loss of mean urinary free cortisol (mUFC) response during R-W (ie, mUFC ≥1.5x ULN or mUFC >40% above baseline if baseline was >1.0x ULN, or other rescue criterion met). Key secondary endpoints include mUFC normalization and changes in comorbidity biomarkers at the end of R-W. Of 84 patients dosed in LOGICS (12 SONICS-completers and 72 de novo), 79 were titrated (72 de novo) and 44 patients (39 from T-M and 5 direct roll-overs from SONICS) were randomized 1:1 to receive levoketoconazole (n=22) at an individualized therapeutic dose or a matching placebo regimen (n=22). The R-W population mean age was 44.3 years, 77% were female, 91% were white, mean weight was 83.2 kg, and 86% had Cushing's disease. Selected results from an interim analysis at the end of R-W are presented. At the end of R-W, significantly more patients on placebo (95.5%) achieved primary endpoint of loss of mUFC response than those who continued on levoketoconazole (40.9%) (treatment difference [TD], -54.5%; 95% CI: -75.7, -27.4; *P*=0.0002). Similarly, the mUFC normalization rate at the end of R-W was significantly higher for levoketoconazole (50.0%) versus placebo (4.5%; TD, 45.5%; 95% CI: 19.2, 67.9; *P*=0.0015). Mean change from R-W baseline to end of R-W in total cholesterol was -1.4 mg/dL for levoketoconazole and +35.6 mg/dL for placebo (*P*=0.0004); mean change in LDL cholesterol was -0.2 mg/dL and +25.0 mg/dL, respectively (*P*=0.0056). Mean change in glycemia markers and high sensitivity C-reactive protein were not significantly different between treatment groups. 90% of levoketoconazole-treated patients across the T-M and R-W phases (n=80) had ≥1 treatment-emergent adverse event (AE); AEs led to treatment discontinuation in 19% (15/80) of patients, 11% (9/80) of which were considered treatment-related. The most common AEs were nausea (29%), hypokalemia (28%), and headache (21%); serious AEs drug related were reported in 4 patients (3 liver-related, 1 gastroenteritis, 1 hypokalemia); AEs of special interest included liver-related (11%), QT prolongation (10%), and adrenal insufficiency (10%). These LOGICS interim results confirm the safety and efficacy findings from SONICS, establishing treatment benefit as levoketoconazole specific. This evidence further supports the use of levoketoconazole as an important treatment option for endogenous CS. **Support:** Strongbridge Biopharma.

Neuroendocrinology and Pituitary
CLINICAL TRIALS AND STUDY UPDATES IN NEUROENDOCRINOLOGY AND PITUITARY

Safety and Efficacy of Switching Injected Peptide Long-Acting Somatostatin Receptor Ligands to Once Daily Oral Paltusotine: ACROBAT Edge Phase 2 Study

Monica R. Gadelha, MD, PhD[1], Murray B. Gordon, MD[2], Mirjana Doknic, MD, PhD[3], Emese Mezősi, MD, PhD, DSci[4], Miklós Tóth, MD, PhD, DSci[5], Harpal Randeva, MBChB, FRCP, FAcadTM, PhD[6], Tonya Marmon, PhD[7], Rosa Luo, MS[8], Michael Monahan, MBA[8], Ajay Madan, PhD[8], Christine Ferrara-Cook, MD, PhD[8], Scott Struthers, PhD[8], Alan Krasner, MD[8].

[1]Neuroendocrinology Research Center/Endocrinology Division--Medical School and Hospital Universitario Clementino Fraga Filho--Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [2]Allegheny General Hospital, Pittsburgh, PA, USA, [3]Clinical Center of Serbia, Belgrade, Serbia, [4]University of Pécs Medical School, Pécs, Hungary, [5]Semmelweis University, Budapest, Hungary, [6]University Hospitals Coventry and Warwickshire NHS Trust, Coventry, United Kingdom, [7]Marmon Biostatistics, Seattle, WA, USA, [8]Crinetics Pharmaceuticals Inc., San Diego, CA, USA.

Patients with acromegaly not cured by surgery are often initially treated with injected peptide long-acting somatostatin receptor ligands (SRLs). Non-peptide small molecules can also activate the somatostatin receptor and do so with a high degree of precision for the target therapeutic receptor subtype. Paltusotine (formerly CRN00808) is a small molecule somatostatin type 2 (SST2) receptor agonist with high oral bioavailability (70%) and pharmacokinetic profile suitable for once daily dosing. In healthy volunteers, paltusotine has been shown to lower growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels. We hypothesized that patients with acromegaly could switch from injected SRLs to once daily oral paltusotine while maintaining baseline IGF-1 levels. ACROBAT Edge (NCT03789656) was a single-arm study designed to evaluate the safety and efficacy of switching from injected SRLs to paltusotine in patients with acromegaly. The primary analysis population consisted of those who had not achieved normal IGF-1 levels despite stable therapy with long-acting octreotide or lanreotide. Eligible patients received their last injection of SRL 4 weeks prior to switching to once daily oral paltusotine monotherapy for a 13-week treatment period. The starting dose of 10 mg per day was uptitrated in 10 mg increments at specified study visits to a maximal dose of 40 mg per day based on protocol specified study drug toleration and IGF-1 criteria. The primary endpoint was change in IGF-1 from baseline to the completion of the 13-week treatment period. Statistical testing was based on non-parametric Wilcoxon Sign Rank test of whether the median change is different from zero. In addition, the rise in IGF-1 during a 4-week washout period was used to provide supportive evidence of efficacy. Twenty-five patients were enrolled in the primary analysis group, three patients discontinued from the study for non-study drug related reasons, two during the treatment period and one during the washout period after completing treatment. The primary endpoint was achieved as paltusotine treatment resulted in no significant change in IGF-1 levels at week 13 compared to baseline [change in IGF-1 =-0.034 (-0.107, 0.107), median (IQR), p>0.6]. Of the 23 patients who completed the dosing period, 20 (87%) achieved IGF-1 levels at the end of treatment that were within 20% of baseline or lower. Median IGF-1 values rose significantly after paltusotine washout (p<0.0001). The most common treatment-emergent adverse events (>10%) included: headache, arthralgia, fatigue, peripheral swelling, paresthesia and hyperhidrosis. There were no discontinuations due to adverse events and no treatment related serious adverse events. These results suggest that patients with acromegaly treated with injected SRLs can switch to oral paltusotine while maintaining IGF-1 and that paltusotine appeared to be well tolerated.

Neuroendocrinology and Pituitary

CLINICAL TRIALS AND STUDY UPDATES IN NEUROENDOCRINOLOGY AND PITUITARY

Safety Results From MPOWERED, a Phase 3 Trial of Oral Octreotide Capsules in Adults With Acromegaly

Pamela Freda, MD[1], Maria Fleseriu, MD[2], Akexander V. Dreval, MD, PhD[3], Yulia Pokramovich, MD[3], Irina Bondar, MD[4], Elena Isaeva, MD, PhD[5], Wenyu Huang, MD, PhD[6], Mark E. Molitch, MD[7], Djuro P. Macut, MD, PhD[8], Nina Leonova, MD, PhD[9], Gerald Raverot, MD, PhD[10], Yossi Gilgun-Sherki, PhD[11], William H. Ludlam, MD, PhD[12], Gary Patou, MD[12], Asi Haviv, DMD[11], Murray B. Gordon, MD[13], Nienke Biermasz, MD, PhD[14], Shlomo Melmed, MB, ChB[15], Christian J. Strasburger, MD[16].

[1]Columbia College of P&S, New York, NY, USA, [2]Oregon Health & Science University, Portland, OR, USA, [3]M.F. Vladimirsky Moscow Regional Research Clinical Institute, Moscow, Russian Federation, [4]Novosibirsk State Medical University, Novosibirsk Oblast, Russian Federation, [5]Interregional Clinical Diagnostic Center, Kazan, Russian Federation, [6]Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [7]Northwestern University Feinberg School of Medicine, Chicago, IL, USA, [8]University of Belgrade, Belgrade, Serbia, [9]Antrium Multidisciplinary Medical Clinic, Barnaul, Russian Federation, [10]Hospices Civils de Lyon, Lyon Cedex 03, France, [11]Chiasma, Inc., Ness Ziona, Israel, [12]Chiasma, Inc., Needham, MA, USA, [13]Allegheny General Hospital, Pittsburgh, PA, USA, [14]Leiden University Medical Center, Oegstgeest, Netherlands, [15]Cedars Sinai Medical Center, West Hollywood, CA, USA, [16]Charite Campus Mitte, Berlin, Germany.

Background: Injectable somatostatin receptor ligands (iSRLs) have been a mainstay in acromegaly treatment. Oral octreotide capsules (OOC; MYCAPSSA®) were recently approved in the United States. Results from the placebo-controlled CHIASMA OPTIMAL and open-label CH-ACM-01 studies showed an OOC safety profile consistent with that of iSRLs with no new or unexpected safety signals. Results of the MPOWERED trial have enabled a comparison of OOC safety and efficacy with iSRLs.
Methods: To enter MPOWERED, patients must have the following: acromegaly diagnosis, biochemical control of acromegaly (insulin-like growth factor I <1.3 × upper limit of normal; mean integrated growth hormone <2.5 ng/mL), and ≥6 months' iSRLs treatment (octreotide or lanreotide). Eligible patients entered a 26-week Run-in phase to determine the effective OOC dose; responders at week 24 then entered a 36-week randomized controlled treatment (RCT) phase receiving OOC or iSRLs. Safety was monitored as adverse events (AEs) in both arms throughout the trial, including the RCT.
Results: In the RCT, incidence of treatment-emergent adverse events (TEAEs) was similar between groups; 39