in the POMC, PCSK1, or LEPR genes. **Methods:** This was an open-label, single-arm, Phase 2 study of setmelanotide in rare genetic diseases of obesity, including proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) heterozygous deficiency obesity (NCT03013543). Patients aged ≥6 years with POMC, PCSK1, or LEPR heterozygous deficiency obesity received once-daily setmelanotide, which was titrated for 4 weeks to establish the therapeutic dose of 3 mg daily. Treatment at the therapeutic dose continued for an additional 12 weeks. The primary endpoint was mean percent change from baseline in body weight at Month 3. Hunger scores and adverse events (AEs) were secondary endpoints. A responder was defined as having ≥5% weight loss from baseline at Month 3. **Results:** A total of 35 patients were included in this analysis, with mean (standard deviation) age of 39.5 (17.6) years and body mass index of 50.3 (9.4) kg/m^2. Across all patients, the mean percent change in body weight from baseline to Month 3 was −3.7% (90% confidence interval [CI], −5.3% to −2.1%; n=35). A total of 34.3% of patients (12/35) achieved the responder threshold of ≥5% weight loss from baseline at Month 3. The mean percent change in body weight from baseline to Month 3 was −10.1% (90% CI, −12.4% to −7.9%; n=12) and −0.4% (90% CI, −1.2% to −0.5%; n=23) for responders and nonresponders, respectively. The mean percent change in most hunger score from baseline to Month 3 was −4.4% (90% CI, −5.7% to −3.2%; n=10) and −2.3% (90% CI, −3.2% to −1.5%; n=23) for responders and nonresponders, respectively. Among responders, 4 (33%) had variants that were considered pathogenic/likely pathogenic per American College of Medical Genetics criteria. All patients experienced at least 1 AE. Overall, the most common treatment-emergent AEs were skin hyperpigmentation (51.4%), nausea (48.6%), and injection site pruritis (37.8%). One patient had serious AEs of acute myocardial infarction and gastrointestinal hemorrhage that were considered unrelated to setmelanotide. No AEs led to death. **Conclusions:** Setmelanotide was associated with reduced body weight and hunger scores in patients with POMC, PCSK1, or LEPR heterozygous deficiency obesity. While the overall mean percent decrease in body weight may have been less than that previously reported in patients with homozygous or compound heterozygous variants, setmelanotide may be a viable treatment option for some patients with POMC, PCSK1, or LEPR heterozygous deficiency obesity.

Pediatric Endocrinology

EMERGING ENDOCRINE THERAPIES ACROSS THE LIFESPAN

Persistent and Stable Growth Promoting Effects of Vosoritide in Children With Achondroplasia for up to 2 Years: Results From the Ongoing Phase 3 Extension Study

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Objectives: Vosoritide is a potent stimulator of endochondral bone growth and is in development for the treatment of achondroplasia, the most common form of disproportionate short stature. We previously reported on a 52-week, phase 3, pivotal study that demonstrated a highly statistically significant improvement in annualized growth velocity (AGV) when vosoritide was compared to placebo in children with achondroplasia aged 5-18 years (Savarirayan et al, Lancet, 2020). This is an analysis of data after an additional 52 weeks of treatment in the ongoing phase 3 extension study. **Methods:** After completion of the phase 3 placebo-controlled study, 119 children were enrolled into the extension study, where they all receive open label 15 μg/kg/day vosoritide. AGV, height Z-score and body proportion ratio were analyzed to assess efficacy of vosoritide in children who were treated with vosoritide for up to 2 years. Fifty-eight continued treatment with vosoritide and 61 switched from placebo to vosoritide. Two participants on continuous vosoritide treatment discontinued before the Week 52 timepoint. Four participants on continuous vosoritide treatment and 7 participants who switched from placebo to vosoritide missed the Week 52 assessment due to Covid-19. **Results:** In children randomized to receive daily vosoritide, baseline mean (SD) AGV was

4.26 (1.53) cm/year. After the first 52 weeks of treatment, mean (SD) AGV was 5.67 (0.98) cm/year. Mean (SD) AGV over the second year was 5.57 (1.10) cm/year. Mean (SD) change from baseline in height Z-score improved by +0.24 (0.31) at Week 52 in the pivotal study and +0.45 (0.56) at Week 52 in the extension study. Mean (SD) upper-to-lower body segment ratio improved with a change from baseline of -0.03 (0.11) at Week 52 in the pivotal study and -0.09 (0.11) at Week 52 in the extension study. In children who switched from placebo to vosoritide after 52 weeks, baseline AGV was 4.06 (1.20) cm/year and 3.94 (1.07) cm/year after 52 weeks on placebo. In the second year, after receiving 52 weeks of vosoritide, mean AGV was 5.65 (1.47) cm/year, the mean (SD) change in height Z-score was +0.24 (0.34), and the change in upper-to-lower body segment ratio was -0.03 (0.08). No new adverse events associated with vosoritide treatment were detected with up to 2 years of continuous daily, subcutaneous treatment. Most adverse events were mild and no serious adverse events were attributed to vosoritide. The most common adverse event remains mild and transient injection site reactions. **Conclusions:** The effect of vosoritide administration on growth as measured through AGV and height Z-score was maintained for up to 2-years in children with achondroplasia aged 5 to 18 years, with an improvement of body proportions.

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EMERGING ENDOCRINE THERAPIES ACROSS THE LIFESPAN

Primary Results From MATCH: A Randomised Controlled Trial in Primary Aldosteronism

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Primary aldosteronism (PA) is now considered the sole, often curable, cause of hypertension in 5-10% of patients. Yet there has been only one RCT, and practice has changed little since the advent of CT scanning. Adrenal vein sampling (AVS) and adrenalectomy remain the standard, invasive interventions, leading to a 50% reduction in pill count as the average clinical improvement. ***Study Design*** In MATCH (*Is Metomidate PET-CT superior to Adrenal vein sampling in predicting ouTCome from adrenalectomy in patients with primary Hyperaldosteronism*), 142 patients, mean age 52, 32% female, 32% of African ancestry, 46% hypokalemic, had both AVS and 11C-metomidate PET CT (MTO) in random order, and were referred for surgery if aldosterone/cortisol ratio differed >4-fold between adequately cannulated adrenal veins, and/or SUVmax on MTO was >1.25 higher, in a definite tumour, than the opposite adrenal. The primary outcome is the proportion of patients in whom adrenalectomy achieved complete or partial biochemical or clinical cure, analysed hierarchically using PASO criteria.[1] Anticipating ~50% incidence of unilateral PA, MATCH is powered to detect 25% superiority of MTO vs AVS, or non-inferiority at a lower-bound CI of -17%. Secondary outcomes include non-randomised comparison of outcomes between unilateral and bilateral PA; prediction of clinical outcome from the home BP (12 readings over 3 days) before and after starting spironolactone 100 mg od for 4 weeks; quality-of-life assessments; and analyses, by RNAseq, of genotype and transcriptomes of 56 of the CYP11B2-positive tumors, correlated with ethnicity and outcomes. **Results:** The analysis set is 75 patients who, on 31 Dec 2020, had undergone adrenalectomy with > 6 months follow-up. 67 patients (89%) had complete biochemical cure following PASO criteria,[1] and 63 (84%) had complete or partial clinical cure. In 39 of the surgical patients, only one of MTO or AVS was scored as high-probability using criteria above. This score was confirmed at the multi-centre, Multi-Disciplinary Team (MDT) meeting which reviewed all MTO scans without knowledge of AVS. In the primary analysis, comparing accuracy of MTO and AVS by McNemar test, the 39 discordant results were allocated as a win to the positive investigation, if the patient was cured, or to the negative investigation, if not cured. 50/56 CYP11B2-positive tumors had a known mutation; the frequency was *CACNA1 D>KCNJ5>ATP1A1>ATP2B3>CTNNB1>GNAQ>CLCN2*, differing between patients whose hypertension was completely or partially cured. Two other tumors had novel gene mutations. Several RNAseq transcripts varied with genotype and outcome, including some encoding measurable, secreted proteins. Full primary and secondary outcomes will be presented.

1. Williams TA, et al. *Lancet Diabetes Endocrinol*. 2017;5:689-699

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Safety Evaluation of the Omnipod® 5 Automated Insulin Delivery System Over Three Months of Use in Adults and Adolescents With Type 1 Diabetes (T1D)

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