Background: In people with overweight or obesity, long-term maintenance of weight loss is challenging. Subcutaneous (s.c.) semaglutide, a glucagon-like peptide-1 analogue, has shown clinically-relevant weight loss in a phase 2 trial in people with obesity. STEP 4 investigated the impact of continued semaglutide 2.4 mg treatment, vs switching to placebo, on maintenance of weight loss in participants who reached 2.4 mg of semaglutide during a run-in period.
Methods: This was a 68-week withdrawal trial (NCT03548987) in 902 subjects aged ≥18 years with body mass index (BMI) ≥30 kg/m^2 (or BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity), without diabetes. Following a 20 week run-in period, 803 subjects who reached the maintenance dose of once-weekly (OW) s.c. semaglutide 2.4 mg were randomized 2:1 to continue treatment with semaglutide 2.4 mg or switch to placebo for 48 weeks, both as adjunct to lifestyle intervention. The primary endpoint was percentage change in body weight between randomization (week 20) and week 68. Confirmatory secondary endpoints included change in waist circumference and systolic blood pressure. Two estimands were defined: treatment policy and trial product; results are presented for the treatment policy estimand, unless stated otherwise.
Results: Mean body weight (±SD) was 107.2 ±22.7 kg at week 0 and 96.1 ±22.6 kg at randomization (week 20; mean change -10.6%). Randomized participants were mostly female (79%) and white (84%); mean age was 46 years and mean BMI was 34.4 kg/m^2. Between weeks 20–68, estimated mean body weight change was −7.9% vs +6.9% for semaglutide 2.4 mg vs placebo (estimated treatment difference [ETD]: −14.8%; 95% confidence interval [CI]: −16.0, −13.5; p<0.0001), and -8.8% vs 6.5%, respectively, for the trial product estimand (ETD: -15.3%; 95% CI: -16.5, -14.1; p<0.0001). For participants randomized to continue semaglutide, the estimated change in body weight from week 0–68 was -17.4% (-18.2% for trial product estimand). Continued semaglutide treatment (weeks 20–68) led to clinically-relevant improvements in waist circumference, systolic blood pressure, BMI, HbA_{1c}, FPG, and lipids (total cholesterol, LDL, VLDL, and triglycerides) vs switching to placebo (p<0.0001 for all). During the run-in period, 5.3% of participants discontinued treatment due to adverse events; during the randomized period, 2.4% (semaglutide) and 2.2% (placebo) discontinued. Nausea, diarrhea and constipation (mostly transient and mild-to-moderate) were the most frequent adverse events with semaglutide.
Conclusion: In adults with overweight or obesity, continued treatment after dose escalation with OW s.c. semaglutide 2.4 mg until week 68 led to clinically-relevant weight loss, while switching to placebo led to significant weight regain; these data underscore the chronicity and relapsing nature of obesity, and the need for continued treatment.

Adipose Tissue, Appetite, and Obesity

WHAT'S NEW IN WEIGHT MANAGEMENT THROUGH THE LIFESPAN?

Weight Loss, Improved Body Composition and Fat Distribution by Tesomet in Acquired Hypothalamic Obesity

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Background: Structural damage to the hypothalamus often results in hypothalamic obesity characterized by rapid and severe weight-gain with increased risk of cardiovascular and metabolic morbidity and mortality. Currently, there are no approved or effective pharmacological treatments and conventional weight management remains largely ineffective. **Objective:** This RCT investigated safety and efficacy of Tesomet (co-administration of 0.5mg tesofensine and 50mg metoprolol) in hypopituitary patients with acquired hypothalamic obesity. **Methods:** Twenty-one (16 females) hypopituitary adults with hypothalamic obesity were randomized to Tesomet or placebo (2:1) for 24 weeks (NCT03845075). Subjects also received diet and lifestyle counselling. Primary endpoint was safety evaluated by change in heart rate, blood pressure and adverse events. Secondary endpoints included changes in anthropometric measures, body composition, corrected QT-interval and arrythmias. **Results:** Subjects had a median (range) age of 50 (25; 70) years and 90% had a BMI ≥30 kg/m^2. Almost half (48%) had a history of craniopharyngioma, 86% had undergone pituitary/hypothalamic surgery, and 52% had irradiation therapy. All received one or more anterior pituitary hormone replacements; 52% had diabetes insipidus. In total, 18/21 subjects completed the study, one without investigational treatment. Three serious adverse events (SAE) were recorded in 2 subjects randomized to Tesomet. Adverse events were otherwise mostly mild (58%), frequently reported were sleep disturbances (62%), dry mouth (46%) and dizziness (46%), known side effects of tesofensine or metoprolol. Four subjects, two in each group, discontinued treatment. Tesomet discontinuation was secondary to anxiety (n=1) or dry mouth (n=1). No significant differences in heart rate or blood pressure were observed between the two groups. At week 24, compared to placebo (weight-loss: -0.3%), Tesomet treatment resulted in additional mean weight-loss of -6.3% (95CI [-11.3%; -1.3%], p=0.017); increase in the proportion of patients achieving >5% reduction in body weight (Tesomet 8; Placebo 1, OR 11.2 [1.0; 120.4], p=0.046); and reduction in waist circumference of -5.7cm ([-11.5; 0.1], p=0.054). Tesomet-induced weight loss was primarily correlated to a reduction in mean (SD) fat mass -5.3kg (5.3) (r^2=0.9, P=0001) and to lesser extent a reduction in lean tissue mass -2.9kg (1.9) (r^2=0.4, P=0.03). Treatment did not affect corrected

QT-interval; mean change from placebo was -1.1ms (95CI [-16.0; 13.9], p=0.882), nor were arrythmias registered during the trial period. **Conclusions:** Tesomet was generally well-tolerated, did not affect heart rate, blood pressure or QTc-interval, and resulted in significant reductions in body weight compared to placebo in this cohort of hypopituitary patients with acquired hypothalamic obesity.
The study was sponsored by Saniona A/S

Adrenal

ADRENAL - BASIC AND TRANSLATIONAL ASPECTS

Acute Transcriptional Effects of Dexamethasone on Mouse Adrenal Gland Transcriptome

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Researchers have long known that dexamethasone causes cellular and functional changes in the adrenal gland. For example, long-term dexamethasone treatment leads to reversible adrenal cortex atrophy. In the adrenal medulla, dexamethasone treatment alters the maturation and function of the neural crest-derived chromaffin cells. Here we aim to study the acute transcriptional effect of dexamethasone on mouse adrenal gland at the transcriptome level. Our data suggested that a one-hour dexamethasone treatment had a cell type-specific effect on the adrenal transcriptome. There were 922 dexamethasone-induced genes and 853 dexamethasone-suppressed genes. GO analysis showed that the upregulated genes were primarily linked to neuronal cell function. Clustered heatmaps further showed that many genes involved in the catecholamine synthesis were upregulated by dexamethasone treatment, whereas most genes involved in the steroidogenesis pathway were downregulated. Interestingly, steroidogenic factor 1 (SF1, encoded by *Nr5a1*), the critical transcription factor that regulates steroidogenesis, had a >2-fold decrease under the one-hour dexamethasone treatment, suggesting a possible mechanism of the acute suppression of steroidogenic activity. Our findings indicate that the acute effects of dexamethasone stimulate catecholamine synthesis in the medulla, whereas steroidogenesis in the cortex is suppressed by dexamethasone.

Adrenal

ADRENAL - BASIC AND TRANSLATIONAL ASPECTS

Androstenedione Is the Preferred Substrate for Cytochrome P450 11β-hydroxylase Leading to the Production of 11β-Hydroxyandrostenedione in the Adrenal Gland

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Adrenal cytochrome P450 11β-hydroxylase (CYP11B1) is a mitochondrial enzyme that catalyzes the final step of glucocorticoid synthesis, converting 11-deoxycortisol (S) and deoxycorticosterone (DOC) to cortisol (F) and corticosterone (CORT), respectively. CYP11B1 is predominantly located in the zona fasciculata of the adrenal gland with studies also showing that CYP11B1 catalyzes the conversion of androstenedione (A4) and testosterone (T) to 11β-hydroxyandrostenedione (11OHA4) and 11β-hydroxytestosterone (11OHT), respectively. Adrenal vein sampling in women has shown that 11OHA4 turnover is high, with a marked increase after treatment with ACTH which is known to upregulate CYP11B1 expression. We hypothesized that CYP11B1's affinity for A4 as a substrate may be favored over glucocorticoids since 11OHA4 is one of the major androgens produced in the adrenalThis study aimed to elucidate the kinetic parameters (K_m and V_{max}) for A4 and T with respect to CYP11B1. A4 and T (0.2 μM to 5 μM) were assayed in HEK-293 cells transiently transfected with CYP11B1 and the adrenodoxin redox partner. Data was used to generate progress curves and fitted to the Michaelis-Menten equation. A4 had the lowest K_m (0.21 μM) with a significantly higher V_{max} (315.77 pmol/min/mg protein) in comparison to T, S and DOC. Results suggest that A4 binds more readily to CYP11B1 resulting in the high turnover of substrate. The androgenic activity of CYP11B1 catalyzed steroid products was determined using a luciferase assay conducted in CV1 cells. Both A4 and 11OHA4 showed no androgenic activity, however, the 11βHSD2 product of 11OHA4, 11-ketoandrostenedione (11KA4), elicited a response at 100 nM. 11OHT was an androgen receptor (AR) agonist, however, exhibiting a lower response when compared to T and 11-ketotestosterone over all concentrations tested (1, 10 and 100 nM). As confirmation of CYP11B1 activity in the adrenal, circulatory steroid levels were determined in healthy female subjects (n=88). CORT, F and 11OHA4 were measured at a frequency of 70–100%, compared to 11OHT (40–70%), while 11βHSD2 activity produced 11KA4 (<10%). In conclusion, the catalytic efficiency of CYP11B1 towards A4 is higher compared to T and the classical substrates. The high substrate affinity and turnover provides evidence for 11OHA4 in adrenal vein samples. Concurrently, our analysis suggests that agonism is diminished by the presence of the C11- hydroxyl group, while AR agonistic activity is gained upon its conversion to a keto group. Furthermore, these androgens could perhaps modulate cortisol production in the adrenal due to potential competition between precursor substrates.

Adrenal

ADRENAL - BASIC AND TRANSLATIONAL ASPECTS

CTNNB1-Mutant Aldosterone-Producing Adenomas With Somatic Mutations of GNA11/GNAQ Have Distinct Phenotype and Genotype