

Title: Prader-Willi Syndrome *GeneReview* — Therapies Under Investigation

Authors: Driscoll DJ, Miller JL, Schwartz S, Cassidy SB

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## **PWS —Therapies Under Investigation**

Since the following studies are still ongoing no conclusions regarding the long-term safety and efficacy can be made at this time.

### **Oxytocin (Syntocinon)**

Individuals with PWS have been found to have a deficit of oxytocin-producing neurons and decreased oxytocin receptor gene function. Swaab and colleagues [1995] reported a deficit in the oxytocin (OT)-producing neurons of the paraventricular nucleus (PVN) in the brain of patients with PWS). Bittel and colleagues [2007] reported decreased oxytocin receptor gene function in PWS. In addition to decreasing appetite, OT is involved in establishing and maintaining social standards. It has recently been shown in a double blind placebo study, that OT administration to adults with PWS significantly decreased depressive mood tendencies and tantrums while increasing trust in others, with data supporting a trend to decrease appetite [Tauber et al 2011]. In a PWS knock-out (KO) mouse model for *Mage12*, a single OT injection at 5 hours of life prevented early death observed in 50% of new-born mice by recovering a normal suck [Schaller et al 2010]. This same group has recently shown that daily administration of OT in the first postnatal week of life in the *Mage12* KO mouse was sufficient to prevent deficits in social behavior and learning abilities later in the adult mutant male mice [Meziane et al 2015].

A Phase 1 double blind, placebo controlled crossover trial of intranasal oxytocin is currently being tested in children ages 5-11 years old in nutritional phases 2b and 3 at three different sites in the USA as part of a pilot grant under the auspices of an NIH funded Rare Disease Center grant with additional grant support from the Prader-Willi Syndrome Association (USA). A total intranasal dose of 16 IU of OT will be given three times during the course of a week-long study. The primary outcome measure is to evaluate the safety of intranasal oxytocin in children with PWS. Secondary outcome measures are to evaluate the effect of IN oxytocin on hyperphagia. Additional outcome measures will evaluate the effects on anxiety, food issues, irritability, social communication and appetite regulating hormones. A group [Einfeld et al 2014] in Australia found no benefit of IN oxytocin in individuals with PWS 12-30 years of age, but the dose these investigators used was much higher than what is being used in the study referenced above.

### **Carbetocin (FE 992097) – Ferring**

Ferring Pharmaceuticals recently finished a Phase 2 randomized, double-blind, placebo-controlled study of intranasal carbetocin in subjects with PWS ages 10-18 years of age and is in the planning stages for a Phase 3 study in the future.. Carbetocin is a selective oxytocin receptor agonist that has 2 amino acid substitutions from the native ligand, oxytocin. Oxytocin is not receptor-selective and, due to its considerable vasopressin V2 receptor activity, it carries the theoretical risk of prolonged antidiuresis

and hyponatremia. Since some subjects with PWS are known to have polydipsia and low baseline serum sodium levels, adding an anti-diuretic increases the risk of serious complications due to hyponatremia. Therefore, a receptor-selective compound might be preferable to avoid these potential side-effects.

The primary objective of the recently completed Phase 2 study was to assess the effect of intranasal carbetocin on hyperphagia behavioral symptoms in subjects with PWS. The secondary objective was to assess the safety and tolerability of IN carbetocin. The study recently finished and the results have not been published yet.

### **Beloranib – Zafgen**

Zafgen Pharmaceutical is conducting a multicenter Phase 3 study to evaluate efficacy and safety of ZGN-440 (beloranib) in obese adolescent and adult subjects with PWS. This is a randomized, double-blind, placebo controlled trial in obese subjects with PWS to evaluate total body weight, food-related behavior, and safety over 6 months. Beloranib is given subcutaneously (SC). The primary outcome measures being evaluated are change in total body weight and change in hyperphagia-related behavior. The secondary outcome measures being evaluated are the lipid profile and total body fat as measured by DEXA.

Beloranib is an irreversible inhibitor of methionine aminopeptidase 2 (MetAP2), one of three distinct mammalian enzymes (designated MetAP1, MetAP2, and MetAP3, accordingly) that are responsible for removing N-terminal methionine residues from newly synthesized proteins. It has been shown in rodents that MetAP2 inhibitors reduce food intake, lower body weight and selectively reduce adipose tissue mass at doses considerably lower than those required to inhibit experimental angiogenesis and tumor growth [Kim et al 2007]. The complete mechanisms by which MetAP2 inhibitors exert anti-obesity effects remain to be fully elucidated. However, MetAP2 inhibitor treatment results in a concerted induction of triglyceride lipolysis, fatty acid oxidation, ketogenesis, and suppression of food intake that appear to be related to reductions in activation status of the ERK stress kinase pathway that is otherwise augmented in the setting of obesity. Reductions in food intake appear to be a consistent feature of treatment in overweight or obese animals at low doses that are free from adverse effects or toxicological findings. A study done in Australia with adult, post-menopausal women also found reduction in weight, hunger and improvement in fatty acid oxidation resulting in a reduction in lipids [Hughes et al 2013]. These results led Zafgen to conduct a proof-of-concept Phase 2 single site, clinical study (ZAF-211) with beloranib in PWS patients which was recently completed. The Phase 2 study was a randomized, double-blind, parallel comparison of each of 2 dose levels of beloranib and placebo in 17 adult subjects with PWS. Subjects received twice-weekly subcutaneous doses of beloranib (1.2 mg or 1.8 mg) or placebo for 4 weeks, followed by 4 weeks of open label extension of 1.8 mg beloranib dosing. All participants were offered 50% increase in daily calorie allowance throughout the trial to place them into positive energy balance and to be more representative of a less well-controlled food environment. The results have not been published, but are in preparation. Based on the preliminary results the company proceeded with the Phase 3 study which is being conducted at 15 academic centers across the USA. However, very recently there were two deaths in the Phase 3 trial due to pulmonary emboli and the FDA has put a hold on this study.

## **RM-493 (Setmelanotide) – Rhythm**

Rhythm is conducting a Phase 2a, randomized, double-blind, placebo-controlled pilot study to assess the effects of RM-493, a melanocortin 4 receptor (MC4R) agonist, in obese subjects with PWS ages 16-65 years old. The purpose of this study is to evaluate the effects of a once daily subcutaneous (SC) injectable formulation of RM-493 in obese subjects with PWS on tolerability, weight loss and hyperphagia-related behavior.

The melanocortins (MCs) are a family of peptide hormones, including adrenocorticotrophic hormone (ACTH),  $\alpha$ -melanocyte-stimulating hormone (MSH),  $\beta$ -MSH, and  $\gamma$ -MSH that are derived from a common precursor, proopiomelanocortin (POMC). The MC system is involved in the regulation of energy homeostasis and body weight [Marks & Cone 2001, Foster et al 2003, Wikberg & Mutulis 2008], as well as steroidogenesis, sexual function, cardio vascular (CV) function, emotional behavior, and the secretion of several endocrine and exocrine factors. Given the various physiological functions that their activation can modulate, the MC receptors represent a therapeutic target for a variety of indications.

Melanocortin type 4 receptors (MC4R) are located in many of the brain regions known to be involved in feeding regulation and have been identified as the dominant MC receptor involved in body weight regulation.[Marks & Cone 2001] When stimulated, the MC4R induces a dramatic reduction in food intake and body weight and increases insulin sensitivity. The manufacturer states that RM-493, a potent selective peptide agonist for the MC4R, has demonstrated high efficacy in reducing body weight and restoring insulin sensitivity in nonclinical models of obesity in rodents, dogs, and non-human primates. RM-493 is an 8 amino acid, cyclic peptide that binds with high affinity to the human MC4R and is efficient in activating MC4R.

According to the manufacturer they have already treated approximately 200 subjects with RM-493. This includes obese (non-PWS) subjects one one cohort of patients with a mutation in one of the MC4R genes. The manufacturer states that these “clinical trials demonstrated promising weight loss with good tolerability.” In one published [Chen et al 2015] crossover study of 12 obese adults received either RM-493 or placebo by continuous subcutaneous infusion over 72 hours. They found that RM-493 significantly increased resting energy expenditure (REE) and preferentially increased fat oxidation in these obese individuals. RM-493 exhibited minimal side effects and no pressor effects.

## **Diazoxide – Essentialis**

This is a single-center, open-label, single-arm study with a double-blind, placebo-controlled, randomized withdrawal extension. Patients (ages 10-22 years) were initiated on a Diazoxide Choline Controlled-Release Tablet (DCCR) dose escalation trial. DCCR targets the ATP-sensitive potassium channel, a metabolically-regulated membrane protein whose modulation has the potential to impact a wide range of rare metabolic, cardiovascular and CNS diseases. The company's rationale for using DCCR is that by hyperpolarizing hypothalamic neurons, whose activity is otherwise impaired by a defective leptin signaling pathway, the drug has the potential to address many of the abnormalities observed in PWS.

Primary outcome measures are evaluating hyperphagia and resting energy expenditure. Other outcome measures include weight, percent body fat and lipids. Diazoxide is a

first line therapy in a range of orphan indications in neonates, children and adults. Over the last 40 years, there have been many peer reviewed publications covering in vitro, animal model, and clinical results with Diazoxide so the safety and tolerability issues with this drug are well known. However, there have been no publications yet with PWS.

### **AZP-531 (Unacylated Ghrelin) – Alizé Pharma**

Alize is sponsoring a Phase 2 trial of AZP-531, a stabilized peptide analog of unacylated ghrelin (UAG) in adult individuals with PWS at three PWS centers in Europe. The sponsor claims that the unique pharmacological profile of AZP- 531 differentiates it from ghrelin antagonists and all existing therapeutic classes. The drug has been shown in Phase 1 trials to improve glycemic control and weight in non-PWS individuals with obesity and type 2 diabetes. The sponsor wants to test the hypothesis that it could be used for treatment of food-related behavior in patients with PWS. According to the sponsor the drug has also been shown to counteract the increase in food intake induced by acylated ghrelin in animal models [Allas & Abribat 2013].

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