## PROTOCOL SYNOPSIS

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| **Study Title** | Intranasal oxytocin to promote weight loss in children, adolescents, and adults with brain tumors and hypothalamic obesity syndrome |
| **Funder** | Doris Duke Charitable Foundation |
| **Clinical Phase** | Exploratory therapeutic trial, Phase II |
| **Study Rationale** | Brain tumors are the most common solid tumor in childhood (37). While rates of survival are improving, severe obesity is a frequent complication, in particular for children with tumors that affect the hypothalamus (32). Oxytocin (OXT) is a hormone that is produced in the hypothalamus (54). Although endocrinologists routinely replace other deficient hormones in children who have brain tumors, it is not current practice to replace OXT. In diet-induced obese non-human primates, chronic exogenous OXT increases total energy expenditure and inhibits food intake (11), two important physiologic targets for the treatment of brain-tumor related obesity (8, 50). In humans, OXT may promote weight loss (88) and has a favorable safety profile in both adults and children (81). Thus, the proposed study has the potential to identify a rational, effective, and safe treatment strategy for a highly morbid condition for which no alternatives currently exist. For extremely obese individuals, obesity may be entrenched and more challenging to address. Thus, anti-obesity interventions may be more effective in individuals who have not yet developed persistent obesity, as is expected given the natural history of this condition. Increased cardio metabolic risk is present even at BMI > 85%ile or BMI > 25 kg/m$^2$. For this reason, we will include overweight and obese individuals. Moreover, the insights gained with respect to the pathophysiology of this highly recalcitrant form of obesity are expected to inform the development of innovative strategies to address other rare human obesity syndromes, as well as the more widespread epidemic of diet-induced obesity in children (61). |
| **Study Objective(s)** | **Primary**<br>• To determine whether 8 weeks of treatment with intranasal OXT **promotes weight loss** in individuals with HypOb syndrome compared to 8 weeks of placebo.<br>**Secondary**<br>• To assess the **safety and tolerability** of treatment with intranasal OXT over this duration<br>• To profile OXT serum levels (pulsatility profiling) following exogenous OXT *vs* placebo during **pharmacokinetic measurements** |

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| | • To assess the impact of OXT on **body composition** and ectopic **muscle fat**.<br>• To test the impact of OXT on **energy intake and cognition at mealtimes**, including calories consumed (test meal, 3-day diet record) and validated measures of cognition and eating behaviors.<br>• To test the impact of OXT on **energy output**, including resting energy expenditure (REE), respiratory quotient (RQ), muscle mitochondrial oxidative phosphorylation (OXPHOS) capacity, body composition and muscle fat, and voluntary physical activity.<br>• To test the impact of OXT on **mental/emotional health** and **family function**, via validated assessments.<br>• To facilitate **future mechanistic studies** by banking biological specimens. |
| **Test Article(s)** | Intranasal oxytocin (Syntocinon, Novartis/Mylan Pharma) is a synthetic form of the hypothalamic hormone. This drug was previously approved in the U.S. for induction of milk let-down and was voluntarily withdrawn for lack of profitability. There were no safety concerns. The drug is currently approved and used for this indication in Europe from where it will be imported for the present study. |
| **Study Design** | Randomized, double-blinded, placebo-controlled, cross-over trial. |
| **Subject Population**<br>**Key Criteria for Inclusion and Exclusion:** | **Inclusion Criteria**<br>1) Proficient in English.<br>2) Males or females age 10 to 35 years, inclusive.<br>3) Weight ≥ 51 kg<br>4) Girls must have a negative urine/serum pregnancy test and post-menarchal girls must use an acceptable method of contraception, including abstinence, a barrier method (diaphragm or condom), Depo-Provera, or an oral contraceptive, for the duration of the study.<br>5) Hypothalamic obesity, defined for the purposes of this protocol as:<br>- previously diagnosed with a brain tumor*<br>- currently overweight or obese (BMI >85%ile for age/sex for < 18 years, BMI > 25 kg/m$^2$ for 18 – 35 years)<br>- has at least one other endocrinopathy, indicating hypothalamic damage |

- rate of annualized weight gain during any 6 month period (given variability in clinical course) preceding or after diagnosis and treatment greater than 2 standard deviations above population reference ranges for age and sex (45).

6) At least 6 months since completion of therapy with stable disease/lack of recurrence.

7) Stable (dose adjustments of ≤ 20% allowed) for at least 2 months on any pituitary replacement (e.g., glucocorticoid, thyroid hormone, estrogen/progestin or testosterone, growth hormone).

   *Desmopressin is not required to be stable for at least 2 months. Even when taken as directed, duration of effect can vary. Participants with DI, taking desmopressin, are required to have intact thirst and be well-controlled on their current dosing regimen.

8) Stable (no dose adjustments) for at least 2 months on any appetite-modulating medications (e.g., stimulants).

9) Be able to ambulate independently.

10) Parental/guardian permission (informed consent) and child assent.

*In hypothalamic obesity related to brain tumors, it is the damage to the hypothalamus caused by the tumor itself, or its treatment (surgery or radiation) that leads to excess weight gain. The majority of such tumors will be craniopharyngioma; a minority will be hypothalamic astrocytomas, germinomas, or other lesions. Given the overall rarity of these tumors, it is not practical to stratify by tumor type or recruit children with only one tumor type. Instead, we will minimize clinical heterogeneity by applying the criteria proposed above with respect to endocrinopathies (indicating hypothalamic damage) and rapid weight gain.

**Exclusion Criteria**

Exclusion criteria and AEs will be defined based on Common Terminology Criteria for AEs (CTCAE), version 4.0 (33).

1) Diabetes insipidus without intact thirst mechanism (i.e., history that participant is not thirsty when hypernatremic and/or continues to be thirsty when hyponatremic, by participant/family and/or practitioner report and medical records) and/or “brittle” diabetes insipidus, defined as requiring >1 admission in the past year and/or any admission within the previous 3 months.

***Laboratory values:*** <130 or >150 mEq/L

2) Diabetes mellitus requiring insulin or insulin secretagogue.

   ***Laboratory values:*** HgbA1c ≥8%

3) Cardiovascular condition, as defined as any of the following: i) abnormal blood pressure, defined as <3%ile or >97%ile for age, sex and height (39) for adult participants abnormal blood pressure is defined as Stage 2 hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg); ii) history of cardiac arrhythmia or arrhythmia detected on screening ECG; iii) history of heart failure and/or cardiomyopathy; iv) prolonged QTc interval (QTc > 460 msec), and/or long QT syndrome phenotype and/or positive genotype for long QT syndrome pathogenic mutations.

4) Concurrent chronic use of medications known to prolong QTc interval and pose high risk for Torsades de Pointes (TdP) according to the current information available (www.crediblemeds.org). Concomitant medications will be assessed by IDS pharmacist, in collaboration with study cardiologist, if additional clarification is needed. In addition, we require that potential participants be on a stable dose for at least 2 months of any medication with the potential to alter cardiac rhythm to ensure the screening ECG reflects steady-state physiology.

5) History of liver disease, with screening laboratory studies:

   ***Laboratory values:*** ALT/SGPT > 3.0X ULN or AST/SGOT > 3.0X ULN

6) History of chronic kidney disease, with screening laboratory studies:

   ***Laboratory values:*** eGFR < 60 mL/min/1.73m$^2$, as defined by the Schwartz formula (71)

7) Clinically significant anemia, with screening laboratory studies:

   ***Laboratory values:*** Hemoglobin < 10 g/dL

8) Seizure in the past 12 months.

9) History of gastrectomy, gastric bypass, small or large bowel resection.

10) History of active substance abuse.

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| | 11) Current psychotic disorder and/or suicidality.<br><br>12) Supra-physiologic (>15 mg/m$^2$/day) prescribed doses of hydrocortisone equivalent.<br><br>13) Anticipated clinical plan to initiate or modify pituitary hormone replacement and/or appetite-modulating drugs during the course of the study, at the time of enrollment. After enrollment, changes to pituitary hormone replacement will be as outline in Section 4.8.<br><br>14) Any investigational drug use within 30 days prior to enrollment.<br><br>15) Pregnant or lactating females.<br><br>16) Individuals with a known sensitivity to either oxytocin or the components of its formulation.<br><br>17) Inability to take an intranasal medication (e.g., recent injury).<br><br>18) Parents/guardians or subjects who, in the opinion of the Investigator, may be non-compliant with study schedules or procedures.<br><br>If vital signs and/or laboratory tests initially indicate ineligibility, select metrics may be repeated, and if eligibility is then demonstrated on repeat, subject will be enrolled. Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures. |
| **Number Of Subjects** | N = 150 enrolled participants (Children's Hospital of Philadelphia); because parents are engaged in research, we anticipate 150 participant-parent/legal guardian dyads, N = 20 participants with complete data. Adult participants, living independently, may enroll individually. |
| **Study Duration** | Each subject's participation will last approximately 7 months.<br>The entire study is expected to last 3 years. |
| **Study Phases**<br>**Screening**<br>**Study Treatment** | Participants will undergo a telephone screening and then, within 4 weeks, complete an in-person screening visit to determine eligibility. Then, within 4 weeks they will be randomized and begin 8 weeks of treatment with either OXT or placebo. After a 4-week "washout," participants will cross-over to 8 weeks of treatment with the other condition (i.e., placebo or OXT). |

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| **Efficacy Evaluations** | Efficacy will be evaluated for each subject by the difference in body weight over the 8 weeks while on OXT versus the 8 weeks while taking placebo. |
| **Pharmacokinetic Evaluations** | During one of the CHPS-monitored doses of each of OXT and placebo, serial peripheral blood measurements of OXT will be made. |
| **Safety Evaluations** | i) Heart rate and blood pressure during CHPS-monitored doses of OXT/placebo; ii) EKG; iii) serum sodium; iv) any need to adjust synthetic vasopressin therapy for diabetes insipidus; v) safety monitoring uniform report form (SMURF) assessments (including potential symptoms such as fluid retention, nausea/vomiting, nasal irritation) |
| **Statistical And Analytic Plan** | The within-subject effect of OXT (versus placebo) on weight change over 8 weeks will be assessed using linear mixed-effects model with the outcome being the difference of the post-treatment weight between two periods (treatment vs. placebo), adjusted for the difference of the baseline weight between the two periods as covariate. |
| **DATA AND SAFETY MONITORING PLAN** | The PI will be responsible for data quality management and ongoing safety assessment. A DSMB will be convened and will meet as per DSMB charter. |