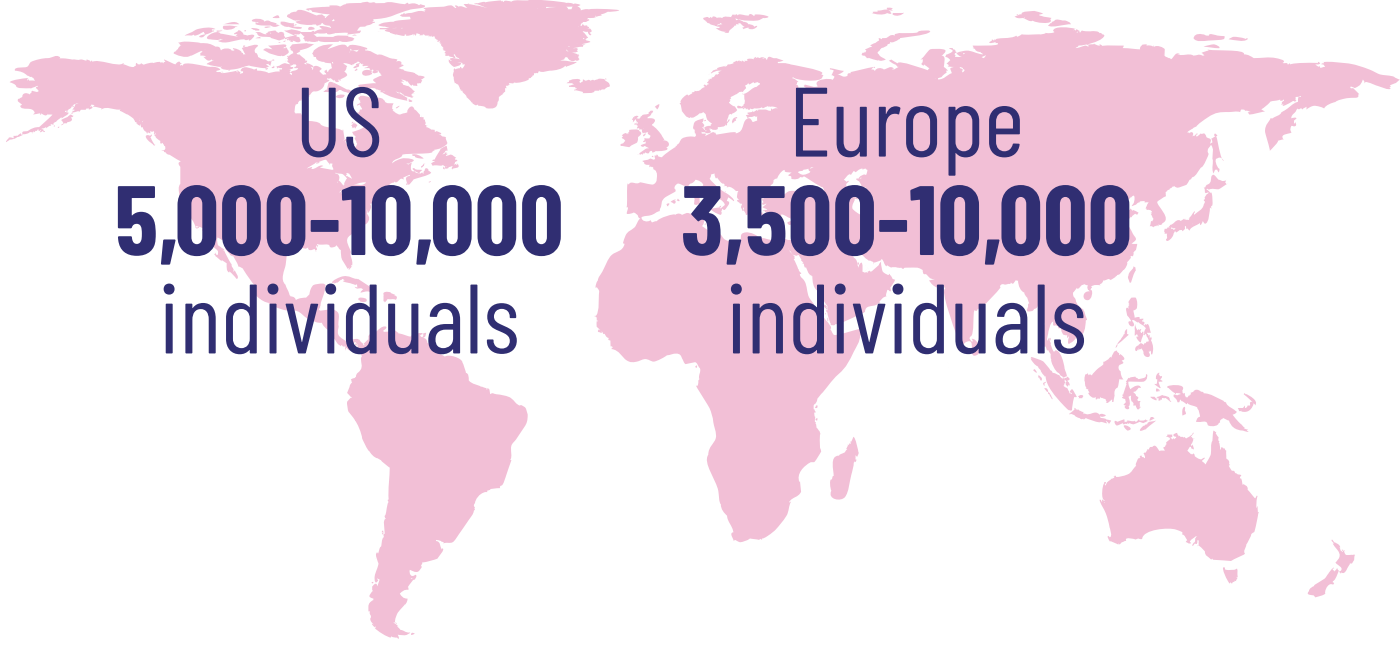
Hypothalamic Obesity

What is Hypothalamic Obesity?

Hypothalamic obesity is an acquired form of rapid-onset, severe obesity that occurs most frequently after hypothalamic damage resulting from surgical resection or radiation of brain tumors[1-3]

Prevalence[4]



(Rhythm Pharmaceuticals estimate)

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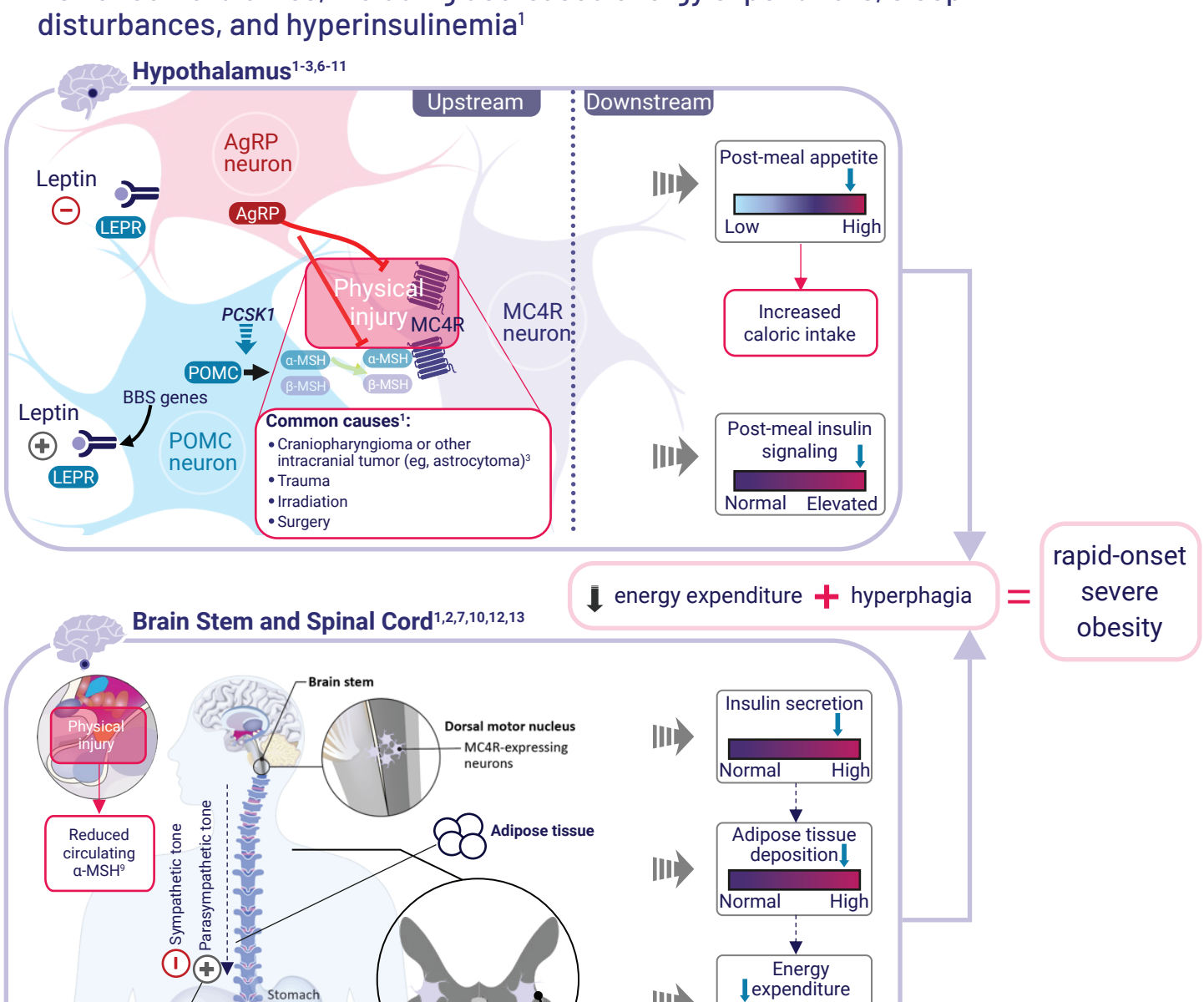
- Injury to the hypothalamic region can impair signaling of the MC4R pathway—a critical regulator of satiety and energy balance—in the hypothalamus, brain stem, and spinal cord.[1-3, 5] Disruption of the MC4R pathway is associated with pathological, insatiable hunger (ie, hyperphagia), severe obesity,[5,6] and increased risk of comorbidities, including decreased energy expenditure, sleep disturbances, and hyperinsulinemia[1]



AgRP, agouti-related protein; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

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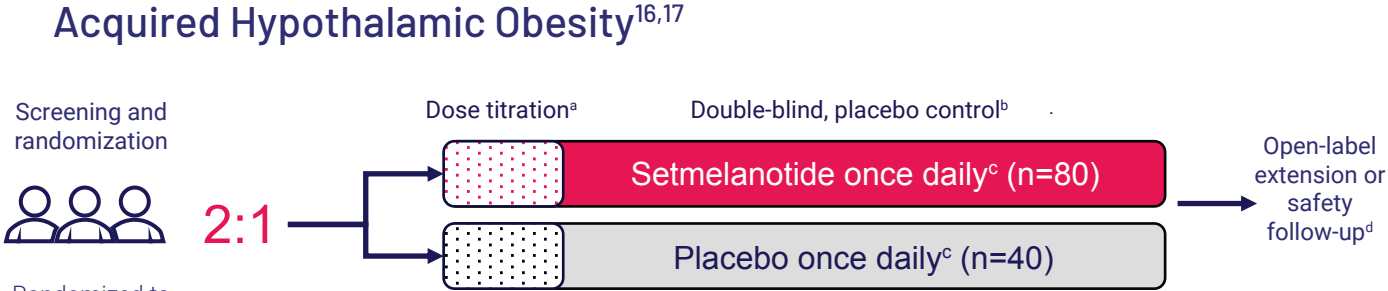
Rapid-onset, severe obesity and hyperphagia observed in hypothalamic obesity are often refractory to traditional weight management strategies[1,5]
Setmelanotide is an MC4R agonist being studied for its effect on weight and hunger in patients with MC4R pathway diseases[14,15]

A Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients With Acquired Hypothalamic Obesity[16,17]



[a]The initial dose of 0.5 mg is to be escalated in increments of 0.5 to 1.0 mg until the patient reaches an individual therapeutic regimen based on age and weight. [b]Patients completing the trial may be eligible to participate in an open-label LTE trial. [c]Subcutaneous injection. [d]The safety follow-up visit is required only for patients prematurely discontinuing treatment or those completing the trial who do not enroll in the LTE.

Key Eligibility Criteria[16,17]

KEY INCLUSION CRITERIA

- ≥4 years of age
- Documented evidence of acquired hypothalamic obesity, defined as
  - Diagnosis of craniopharyngioma or other brain lesion affecting the hypothalamic region with treatment (ie, surgery, chemotherapy, radiation) received ≥6 months before screening
  - Documented injury to the hypothalamus ≥6 months before screening for which surgery or radiation is not indicated
- Documented weight gain associated with hypothalamic injury (before or after therapy), and
  - BMI ≥30 kg/m^2 for those aged ≥18 years
  - BMI ≥95th percentile for age and sex for those aged <18 years

KEY EXCLUSION CRITERIA

- Diagnosis of PWS or ROHHADNET syndrome
- Obesity due to genetic or syndromic conditions before hypothalamic injury
- Weight loss in the prior 3 months
  - >2% reduction in body weight for those aged ≥18 years
  - >2% reduction in BMI for those aged <18 years
- Bariatric surgery or procedure within the last 2 years
- HbA_{1c} >11.0%
- Significant dermatologic findings relating to melanoma, or a history or close family history of skin cancer or melanoma
- Severe psychiatric disorder or major depressive disorder

BMI, body mass index; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; LTE, long-term extension; PWS, Prader-Willi syndrome; ROHHADNET, rapid-onset obesity with hypoventilation, hypothalamic dysfunction, autonomic dysregulation, and neuroendocrine tumor.

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Key Endpoints[16,17]

Approximately 120 patients will be enrolled across **up to 35 sites globally**

PRIMARY ENDPOINT[a]:

- Mean percentage change in BMI

KEY SECONDARY ENDPOINTS[a]:

- Composite proportion of patients with ≥5% reduction in BMI (≥18 years of age) and BMI z-score reduction of ≥0.2 points (<18 years of age)
- Proportion of all patients with ≥5% reduction in BMI
- Mean change in weekly average of daily most hunger score in those aged ≥12 years

Safety and tolerability will be assessed by the frequency and severity of adverse events, as well as changes in ambulatory blood pressure and heart rate

[a]After 52 weeks of setmelanotide vs placebo.

Expected Trial Completion Date: April 2025[16]

- For additional trial information, including a list of eligibility criteria and endpoints, please visit https://clinicaltrials.gov/ct2/show/NCT05774756
- For questions about the trial, please contact us at clinicaltrials@rhythmtx.com

Scan to view the ClinicalTrials.gov page

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