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BRIGHT MINDS

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Selective 5-HT$_{2C}$ Agonist BMB-101 in the Treatment of Patients with Prader-Willi Syndrome (PWS)

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Background

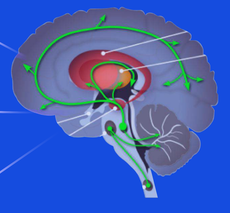
- PWS is a rare neurodevelopmental disorder caused by the loss of expression of paternally inherited genes on chromosome 15q11-q13
- PWS is a complex neurodevelopmental and neurobehavioral disorder, leading to a range of problems including hypotonia in early life, extreme hyperphagia, and behavioral issues such as anxiety, temper tantrums, rigidity of thought and obsessive-compulsive thinking
- The serotonin 2C receptor (5-HT$_{2C}$ receptor) plays a key role in regulating appetite, energy homeostasis, mood, and impulsivity
  - An exploratory assessment of serum prolactin levels
  - An exploratory quantitative electroencephalogram (qEEG) assessment

Serotonin Pathway

Executive functions: cognitive and behavioural issues

Reward system: hyperphagia

Satiety centre: obesity



- Hyperphagia
- Obesity
- Feeding problems
- Compulsion
- Sleep Disturbances
- Aggression
- Cognitive impairment
- Self-injury
- Anxiety
- Epilepsy
- Higher Risks of death
- Psychosis and other psychiatric disorders

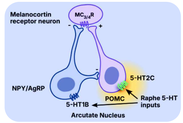
Better therapies needed

Current treatment options for patients with PWS are inadequate as they do not fully address all symptoms; better therapies are needed

Energy balance	Neuropsychiatric symptoms	
Obesity — Glutides	Compulsion	Cognitive impairment
Hyperphagia — Vykat	Sleep Disturbances	Self-injury
Feeding problems	Aggression, Epilepsy	Anxiety — SSRIs
Growth hormone deficiency — hGrh	Higher Risks of death	Psychosis and other psychiatric disorders — AAs

Scientific Rationale

5-HT$_{2C}$ agonism directly targets underlying pathophysiology PWS

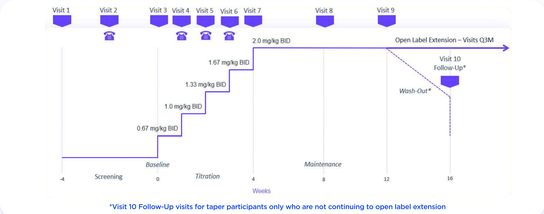


- 5-HT$_{2C}$ receptors are apex regulators of the neuroendocrine axis
- 5-HT$_{2C}$+ neurons project to hypothalamic melanocortin neurons to suppress food intake thereby directly regulating satiety and appetite
- 5-HT2C receptors are also involved in the regulation of compulsive behavior
- PWS patients with PWS express lower levels of mature, functional, 5-HT$_{2C}$ receptors resulting in unabated appetite and compulsive behavior
- 5-HT$_{2C}$ agonist may compensate for loss of 5-HT tonus through the 5-HT$_{2C}$ receptor, thereby treating both hyperphagia and the neurobehavioral symptoms associated with PWS

BMB-101 preclinical findings related to PWS

Hyperphagia	Reduces binge eating and weight loss in rat model
Aggression	Reduces aggressive behaviors in resident intruder mice model
Cognitive improvements	Protects mice from cognitive impairment in the radial arm water maze
Agitation and hyperactivity	Reduces hyperactivity in mice in open field
Uncontrolled cravings Compulsive behaviors	Reduces fentanyl seeking behavior and reduces total doses of fentanyl in an opioid use rat model

Clinical Study of BMB-101 in Patients with PWS



*Visit 10 Follow-Up visits for taper participants only who are not continuing to open label extension

Dosing

- BMB-101 oral liquid or placebo
- Weight-based dosing, with an initial dose of 0.67 mg/kg twice daily (BID) for the first 7 days
- The dose may be titrated in 0.33 mg/kg increments if well tolerated
- The maximum dose is not to exceed 2.0 mg/kg BID based on weight
- For participants not proceeding to the open-label extension study, study drug will be tapered over a 4-week period

Objectives

Primary

- To assess the effect of BMB-101 on hyperphagia-related behaviors in patients with PWS

Secondary

- To assess the effect of BMB-101 on various associated behavioral disorders in PWS
- To assess the safety and tolerability of BMB-101 in patients with PWS

Eligibility criteria

Inclusion criteria

- Men and women aged 18-65, inclusive
- Genetically confirmed diagnosis of PWS via standard DNA testing or other commonly approved methods
- Willing and able to provide voluntary written informed consent, or have a Legally Authorized Representative provide consent
- Participant and/or caregiver can comply with study requirements
- If a caregiver assists in completion of questionnaires, the same caregiver is available to complete the questionnaires throughout the duration of the study
- Moderate to severe hyperphagia as defined by a Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score >13 at time of randomization
- If receiving growth hormone, must be on the same medication and stable dose for at least 90 days prior to Visit 1
- Women of childbearing potential must have a negative urine pregnancy test at Visit 1

Exclusion criteria

- Use of metabolic agents known to affect appetite within 3 months of Visit 1
- Use of psychotropic medications including selective serotonin reuptake inhibitors/serotonin–norepinephrine reuptake inhibitors, monoamine-oxidase inhibitors, tricyclic antidepressants, other serotonergic agonists or antagonists (antipsychotics), and other agents which have known Serotonin Syndrome risk (i.e., mirtazapine) within 1 month of Visit 1
- Implementation of new food restrictions or new environmental restrictions within 1 month of Visit 1
- Participation in an interventional clinical trial of any PWS agent within 3 months of Visit 1 or any other investigational agent within 1 month of Visit 1
- Current or history of cardiovascular or cerebrovascular disease
- Moderate or severe hepatic impairment
- Severe renal impairment
- Clinically significant electrocardiogram abnormality
- History of drug or alcohol abuse within the last 12 months or a positive urine drug screen
- Current Columbia-Suicide Severity Rating Scale (C-SSRS) score of 4 or 5 at Visit 1 or history of suicide attempt at any time during the past year
- Clinically significant condition or has had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to Visit 1, other than PWS, that would negatively impact study participation, collection of study data, evaluation of study endpoints or pose a risk to the participant, in the opinion of the Investigator.
- Pregnant or lactating woman
- Any condition considered to be a degenerative neurological disease

Endpoints

Primary endpoint

- **Hyperphagia:** Change from baseline in HQ-CT scores over time

Secondary endpoints

- **Hyperphagia:** Change from Baseline in hyperphagia severity score as measured by the Caregiver Global Impression of Severity 7-point scale over time
- **Hyperphagia:** Change from Baseline in hyperphagia severity score as measured by the Clinician Global Impression of Severity (CGI-S) 7-point scale over time
- **Global Impression:** Change from Baseline in severity and improvement of PWS disease scores as measured by the CGI-S and Clinician Global Impression of Improvement 7-point scale over time
- **Behaviors:** Change from baseline in PWS-associated behavioral issues such as symptoms measured by the PWS Profile over time

Exploratory endpoints

- Change in weight over time
- Change in ghrelin levels over time
- Change in oxytocin levels over time

Safety endpoints

- Adverse events
- Vital signs
- Physical examination findings
- Safety laboratory tests
- C-SSRS

Pharmacokinetic endpoints

- Serum concentrations of BMB-101 at Visit 7 and Visit 9

Conclusions

This Proof-of-Pharmacology Phase 2a study is the first trial to evaluate the effects of selective 5-HT$_{2C}$ agonist in Prader Willi Syndrome

Evidence to date suggests that BMB-101 has the potential for a best-in-class mechanism of action targeting all major PWS symptoms

Clinical 5-HT$_{2C}$ agonists

- Previously approved as weight loss drugs (lorcaserin and fenfluramine)
- Fenfluramine reduced hyperphagia and improved behaviors in a pilot clinical trial in PWS

Preclinical BMB-101

Efficacy in multiple animal models of:

- Hyperphagia
- Weight loss
- Aggression control
- Impulsivity control
- Cognitive decline

Clinical BMB-101

- Severely overweight (>100kg) patients in epilepsy trial lost >10% weight
- Reported improved relationship with food and overall quality of life
- 24h EEG demonstrate REM sleep improvements

References

1. Dai et al. Rare Dis Orphan Drugs J. 2024;3:33
2. He et al. Nat Med. 2022;28(12):2537-46