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Phase II study to assess the efficacy and safety of pasireotide in patients with post-bariatric hypoglycaemia: PASIPHY study design

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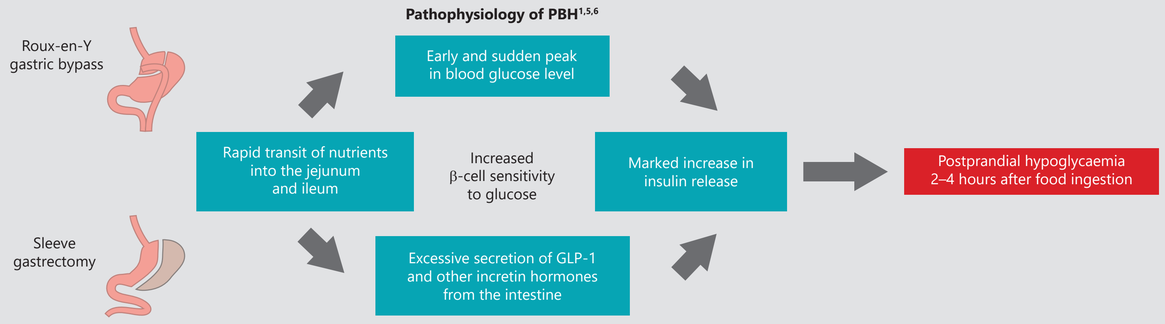
SUMMARY

- **Challenges associated with the management of PBH include the unmet medical need for effective, tolerable and approved therapies[1]**
- **Pasireotide treatment has previously been shown to be effective at suppressing hypoglycaemia in patients with PBH,[2–4] indicating its potential as a promising treatment for patients with PBH**
- **The PASIPHY study will provide valuable data on the efficacy and safety of pasireotide sc in patients with PBH. It will ascertain which dose has the best benefit:risk ratio and determine whether it is a viable treatment option for patients with PBH**

INTRODUCTION

- Bariatric surgery, such as Roux-en-Y gastric bypass or sleeve gastrectomy, is used as a treatment for obesity, diabetes and other metabolic complications owing to the benefits it provides relating to weight loss and diabetes control[1,5]
- PBH occurs after up to 38% of gastric bypass and 12% of vertical-sleeve gastrectomy surgeries and usually presents 1–5 years after bariatric surgery, often after weight stabilisation[5–7]
- PBH is characterised by postprandial hyperinsulinaemic hypoglycaemic episodes, which may consist of dizziness, flushing, fatigue, confusion, palpitations and blurred vision. These symptoms can occur in association with serious neuroglycopenic events such as loss of consciousness and seizures, which may result in serious accidents[1,5,6]

Pathophysiology of PBH[1,5,6]

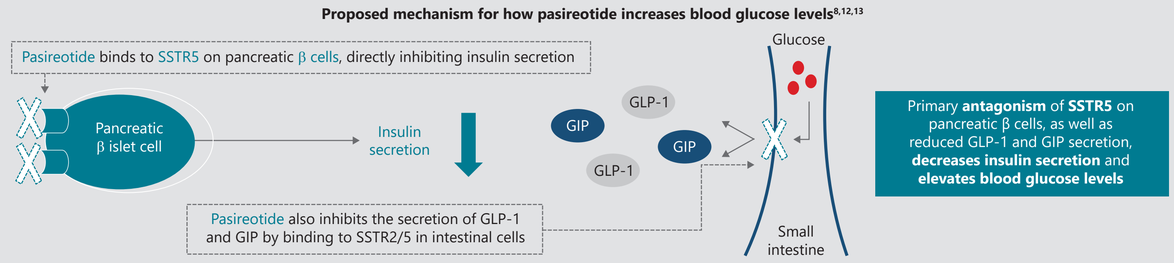


- Dietary modification is considered the mainstay of treatment, although it is not effective for all individuals, and adherence to this strategy is often inadequate in the long term. Add-on treatments are also used for symptom control by targeting the pathophysiological mechanisms, although there are no approved medical therapies[1,6]
- The UK Society of Endocrinology guidelines for the management of PBH highlight the lack of clinical evidence for effective treatments and call for more controlled trials[1]
- **Pasireotide in Postprandial Hypoglycaemia (PASIPHY), a Phase II, dose-finding study (NCT05928390), will assess the efficacy and safety of pasireotide sc treatment in patients with PBH**

RATIONALE FOR PASIREOTIDE TREATMENT IN PBH

- Pasireotide is an injectable somatostatin receptor ligand (SRL) approved in 2012 for the treatment of adults with Cushing's disease (sc formulation), and subsequently for acromegaly and Cushing's disease (LAR formulation), among patients in whom pituitary surgery is not an option or has not been curative (and who are inadequately controlled with another SRL [EU; acromegaly])[8,9]
- Pasireotide binds to four of the five human SSTRs (SSTR1, -2, -3 and -5) and has higher affinity for SSTR5 than other SRLs do; activity at SSTR5 impacts insulin and incretin levels and the rate of gastric emptying[10,11]

Proposed mechanism for how pasireotide increases blood glucose levels[8,12,13]



- In a multicentre, Phase II study,[2] the efficacy and safety of pasireotide sc was evaluated in patients with dumping syndrome who had a documented history of hypoglycaemia or ≥1 glucose measurement <60 mg/dL (<3.3 mmol/L) during an OGTT at screening
  - At the end of a 3-month dose-escalation phase (pasireotide 50–200 µg tid), 60.5% (n=26/43) of patients had plasma glucose ≥60 mg/dL at all OGTT measurement time points over 3 hours
  - Furthermore, during OGTT and compared with baseline, there was:
    - An increase in glucose levels at all time points
    - A decrease in insulin levels during the first 90 minutes
    - A decrease in glucagon, GLP-1 and GIP levels at all time points
    - An improvement in quality of life
  - The clinical benefits of pasireotide treatment were accompanied by a manageable safety profile[2]
- Other studies have demonstrated the benefit of SRLs in hypoglycaemic patients,[14,15] including a small randomised crossover study (n=11)[3] in which pasireotide treatment increased nadir glucose levels in patients with PBH, while a case report[4] concluded that pasireotide resulted in more favourable glycaemic control during MMTT than did octreotide

METHODS

1. In PASIPHY, ~72 patients with PBH will be randomised across ~30 sites in Europe and the USA

Patient inclusion criteria:

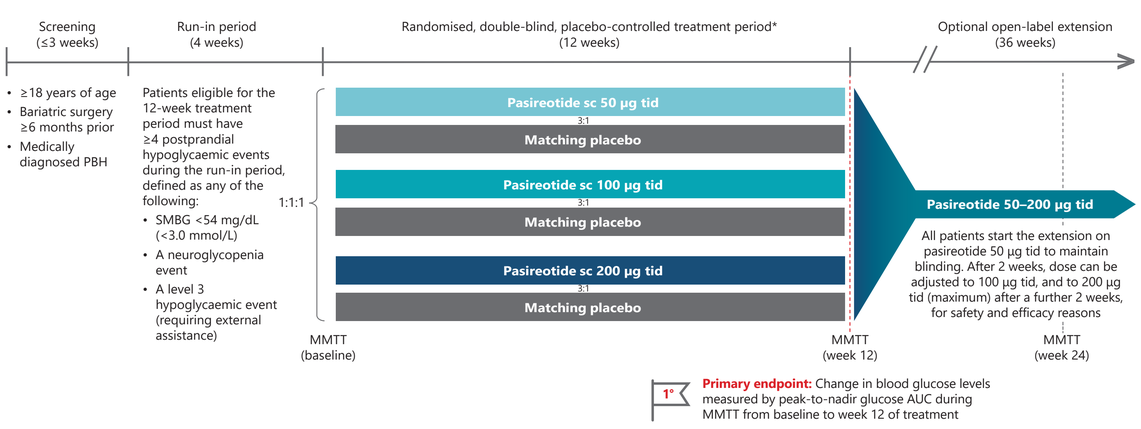
- ≥18 years of age
- Bariatric surgery ≥6 months prior to screening
- Medically diagnosed PBH and a documented glucose measurement of <70 mg/dL (<3.6 mmol/L), with symptoms of hypoglycaemia and resolution following administration of rescue carbohydrates
- Dietary modification insufficient to control PBH symptoms
- Patients who have received other therapies for PBH must have stopped these treatments, including acarbose, guar gum, pectin, diazoxide, GLP-1 receptor antagonists and agonists, and SGLT2 inhibitors
- Capable of self-injecting subcutaneously

Selected patient exclusion criteria:

- Patients with a lap band
- Current diagnosis of uncontrolled diabetes mellitus
- Patients with hypocortisolism
- History of, or current, insulinoma
- Patients fulfilling protocol-defined bradycardia and QT interval related criteria

2. PASIPHY comprises a ≤3-week screening, a 4-week run-in and a 12-week randomised, double-blind, placebo-controlled treatment period in its core phase

- Patients eligible for the 12-week treatment period must have ≥4 postprandial hypoglycaemic events during the run-in period (described in the study design figure)
- Patients will be randomly allocated to pasireotide sc or matching placebo tid, in a 3:1 ratio
  - Patients randomised to pasireotide sc will receive 50 µg, 100 µg or 200 µg tid
- Those completing the 12-week core phase can choose to receive pasireotide during a 36-week open-label extension



*Patients randomised to receive pasireotide 100 µg or 200 µg tid will initiate treatment with 50 µg tid; among these patients, the dose will be increased on day 5 to 100 µg tid, and on day 9 to 200 µg tid for those randomised to the 200 µg tid treatment arm

3. The primary objective of PASIPHY is to evaluate the efficacy of pasireotide sc with respect to blood glucose concentration during a 3-hour MMTT in patients with PBH

1° Primary endpoint	Change in blood glucose levels measured by peak-to-nadir glucose AUC during MMTT from baseline to week 12 of treatment

- Primary completion is expected by Q1 2026

MMTT

- Conducted between 07:00 and 10:00 after an overnight fast (≥8 hours)
- Patient drinks standardised liquid meal (commercially available formula)
- Blood samples for glucose measurement taken 10 minutes prior to pasireotide administration and meal uptake, then at the following time points: 0, 30, 60, 90, 105, 120, 135, 150, 165 and 180 minutes
- Patients observed for symptoms and/or signs of hypoglycaemia at each time point

4. PASIPHY secondary endpoints will evaluate level 2 and level 3 hypoglycaemic events, the use of rescue therapy, and change from baseline in insulin, glucagon, and GLP-1 secretion, as well as change in pulse rate and haematocrit, during the MMTT. HRQoL will also be evaluated at various time points, while incidence of AEs and laboratory values will be assessed throughout the study

Secondary endpoints	Core phase: Treatment week of endpoint assessment	Extension phase: Treatment week of endpoint assessment
Change from baseline in rate of level 2 hypoglycaemic events (SMBG)	Weeks 4, 8 and 12	Weeks 16, 20, 24, 32, 40 and 48
Proportion of patients with no level 2 hypoglycaemic events during 3-hour MMTT	Week 12	–
Change from baseline in rate of level 3 hypoglycaemic events	Weeks 4, 8 and 12	Weeks 16, 20, 24, 32, 40 and 48
Change from baseline in rate of level 2 hypoglycaemic events lasting at least 15 minutes (CGM)	Weeks 4, 8 and 12	Weeks 16, 20, 24, 32, 40 and 48
Change from baseline in the duration of level 2 hypoglycaemic events lasting at least 15 minutes (CGM)	Weeks 4, 8 and 12	Weeks 16, 20, 24, 32, 40 and 48
Change from baseline in percentage time with level 2 hypoglycaemic events (CGM)	Weeks 4, 8 and 12	Weeks 16, 20, 24, 32, 40 and 48
Change from baseline in frequency of use of rescue therapy and/or rescue carbohydrates at home to manage level 2 hypoglycaemic events	Weeks 4, 8 and 12	Weeks 16, 20, 24, 32, 40 and 48
Change from baseline in frequency of use of rescue therapy and/or rescue carbohydrates at home to manage level 3 hypoglycaemic events	Weeks 4, 8 and 12	Weeks 16, 20, 24, 32, 40 and 48
Proportion of patients with change in pulse rate <10 bpm during MMTT	Week 12	Week 24
Proportion of patients with change in haematocrit <3% during MMTT	Week 12	Week 24
Absolute and percentage changes in insulin, glucagon and GLP-1 secretion from baseline during MMTT	Week 12	Week 24
Change from baseline in HRQoL (SF-36 score, Hypoglycaemia Fear Survey II, Dumping Score Questionnaire and Patient Global Assessment)	Week 12	Weeks 24 and 48
Incidence of AEs, laboratory and ECG findings, and change from baseline in laboratory values, ECG readings, gallbladder imaging, and vital signs	Throughout	Throughout

- Throughout the study, a CGM device will report sensor glucose level every 5 minutes; an alarm will inform the patient when sensor glucose levels decrease to <54 mg/dL (<3.0 mmol/L), at which point, the patient should use a glucometer (SMBG) to confirm the level of glucose
  - Patients with confirmed glucose <54 mg/dL (<3.0 mmol/L) should take rescue carbohydrates or medication

Pharmacokinetic objective	Evaluate the pharmacokinetic profile of pasireotide in patients with PBH

- C_{max}, t_{max} and $AUC_{0–t}$ will be determined by non-compartmental analysis during MMTT at treatment weeks 12 and 24

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DISCLOSURES

PASIPHY is funded by Recordati Rare Diseases.

ABBREVIATIONS

AE, adverse event; AUC, area under the concentration–time curve; $AUC_{0–t}$, area under the concentration–time curve from time 0 to t; CGM, continuous glucose monitoring; C_{max}, maximum serum concentration; ECG, electrocardiogram; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; HRQoL, health-related quality of life; LAR, long-acting release; MMTT, mixed-meal tolerance test; OGTT, oral glucose tolerance test; PBH, post-bariatric hypoglycaemia; Q1, first quarter; sc, subcutaneous; SF-36, Short Form 36; SGLT2, sodium–glucose co-transporter 2; SMBG, self-monitored blood glucose; SSTR, somatostatin receptor; SRL, somatostatin receptor ligand; tid, three times daily; t_{max}, time to reach maximum concentration

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