# Participant-Informed Design Considerations in Phase 3 LUCIDITY Trial of Avexitide for Post-Bariatric Hypoglycemia

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ENDO TOPICAL CATEGORY: DIABETES AND VASCULAR DISEASE

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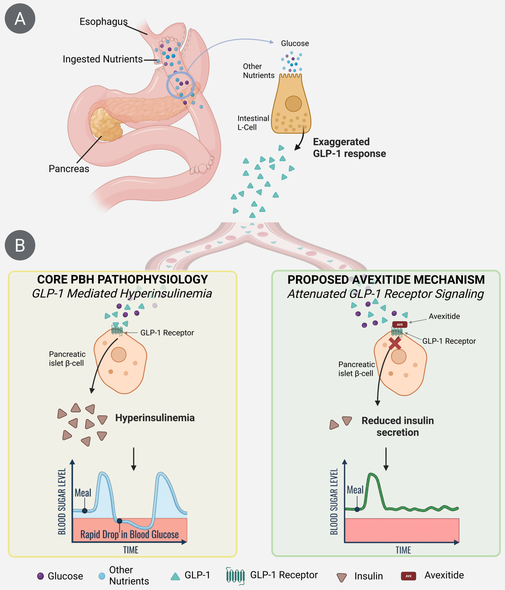
## BACKGROUND & SELECT PRE-TRIAL INSIGHTS

- Post-bariatric hypoglycemia (PBH) is a chronic metabolic condition that can develop after metabolic and bariatric surgery, characterized by **recurrent postprandial hyperinsulinemic hypoglycemia**[1-5] (Figure 1)
- Episodes are often **unpredictable and can impair daily functioning and markedly diminish quality of life**[4] (Figure 2)
- An **exaggerated GLP-1 response** is a key driver of postprandial insulin hypersecretion in PBH[1-3]
- Despite substantial clinical burden, there are currently **no approved pharmacologic therapies specifically for PBH**
- **Avexitide is a potential first-in-class GLP-1 receptor antagonist** that attenuates GLP-1 receptor signaling and has been shown to reduce GLP-1-mediated insulin hypersecretion[6,9,12] (Figure 1)
- Across 5 prior PBH trials, **statistically significant and clinically meaningful reductions in hypoglycemia were observed; avexitide demonstrated a favorable safety profile** with generally mild to moderate, transient adverse events and no treatment-related serious events or discontinuations[6-14]
- Based on mechanistic rationale and previous clinical study results, avexitide is currently under study in the Phase 3 LUCIDITY trial for PBH (Figure 3)

### Figure 1. Core PBH Pathophysiology & Avexitide Mechanism of Action




*(A) Following MBS, altered nutrient transit leads to an exaggerated GLP-1 response, leading to postprandial hyperinsulinemia and hypoglycemia[8-9]*

*(B) Avexitide is proposed to attenuate GLP-1 signaling, reducing hyperinsulinemia and mitigating hypoglycemia[5-7,12-14]; glucose curves shown are illustrative and do not represent actual blood glucose measurements*

### Figure 2. Pre-Trial Insights from People with PBH[15]

*These insights directly informed key elements of LUCIDITY study design and endpoint strategy*

**LIVING WITH PBH**

***Severity is functional, not solely numeric***

- Recurrent, unpredictable highs and lows
- Functional and cognitive impairment, not glucose thresholds alone, define severity
- Daily safety can depend on real-time monitoring via SMBG and CGM trends and alarms

**CONSIDERING TRIAL PARTICIPATION**

***Safety drives willingness***

- Important to consider monitoring and unrecognized hypoglycemia
- Study safeguards should reflect real-world risk
- Critical that hypoglycemia definitions capture lived experience

**ANTICIPATED TRIAL EXPERIENCE**

***Monitoring supports safe management***

- Monitoring requirements must not increase cognitive load and anxiety
- Events often follow glycemic swings, not isolated lows
- Clear guidance needed for reporting and response

**POTENTIAL FOR BENEFIT & EXPECTATIONS**

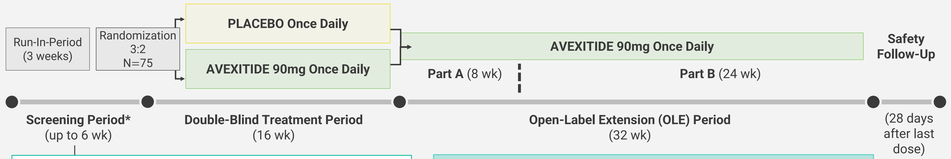
***Benefit must translate to daily life***

- Hypoglycemia reduction is key; additional outcomes valued by participants
- Importance of increasing confidence in daily activities
- Managing hypoglycemia leads to predictability and restoring more normalcy

## OBJECTIVE

To describe the LUCIDITY trial design, highlighting participant-informed design considerations and the endpoint strategy selected to capture the clinical and participant-reported burden of PBH

### Figure 3. LUCIDITY Trial Designed to Capture Clinically Meaningful Hypoglycemia Using Integrated CGM, SMBG, and Adjudication




Key Trial Entry Criteria:

- Roux-en-Y gastric bypass (RYGB) ≥12 months prior to screening
- Clinical diagnosis of PBH
- ≥3 hypoglycemic events during the 3-week run-in (Level 2 or 3, including ≥1 Level 3 event)

**STUDY STATUS:**
Enrollment complete; double-blind phase is ongoing
**Topline data expected Q3 2026**

## KEY TAKEAWAYS

- **PBH burden is multidimensional**, extending beyond glucose thresholds to functional disruption, safety concerns, and cumulative daily impact
- **Participant-reported experience paired with clinician feedback directly informed LUCIDITY trial design**, including monitoring strategy, safety oversight, and feasibility considerations
- **Hypoglycemia endpoints were selected to reflect meaningful clinical impact**, integrating glucose levels, hypoglycemia symptoms, and participant-reported outcomes
- **LUCIDITY represents the first Phase 3 evaluation of a targeted GLP-1 receptor antagonist** designed to address a core mechanistic driver of PBH

## OPERATIONAL DESIGN TO SUPPORT MEANINGFUL OUTCOME CAPTURE

### Trial Execution

- Standardized training to align sites on PBH risk, event recognition, and protocol execution
- Standardized training and support for participants to collect decentralized continuous data via remote data acquisition tools
- Independent adjudication of hypoglycemic events using consistent, predefined criteria

### Participant-Centered Design

- Plain-language participant guide and early study orientation to reduce uncertainty
- Integrated CGM, SMBG, and e-diary strategy to support real-time event detection
  - > Unlimited SMBG monitoring
  - > Pre-specified alarms and clear guidance for symptom recognition and reporting
  - > Unblinded CGM included in OLE Part B
- Optional support services (e.g., logistical assistance, participant support resources, and flexible visit options) to reduce participant burden
- Open-label extension conducted under the study protocol to support continued participation and data collection
- Expanded Access Program (EAP) available to support continued access following trial participation

### Endpoint & Assessment Strategy to Capture the Multidimensional Lived Burden of PBH

**Hypoglycemia Burden**
Composite of clinically meaningful events informed by glucose thresholds, symptoms, and adjudication

**Glycemic Patterns & Variability**
CGM-derived measures of glycemic variability and glucose excursions to gain additional insight into patterns over time

**Participant-Reported Impact**
eDiary, qualitative interviews, and quality-of-life measures capturing functional disruption and daily impact

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**Avexitide is an investigational drug and has not been approved for use by any health authority (e.g., the FDA).**

**Definitions & Abbreviations**

GLP-1, glucagon-like peptide-1; SMBG, self-monitoring of blood glucose; CGM, continuous glucose monitoring; MBS, metabolic and bariatric surgery

Hypoglycemia Definitions: Level 2 – Glucose <54 mg/dL (3.0 mmol/L). Captured in LUCIDITY via SMBG; Level 3 – A severe event characterized by altered mental and/or physical status requiring assistance. Captured in LUCIDITY by eDiary and adjudicated by the independent Event Adjudication Committee

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**Disclosures**

**MT** reports consulting fees and scientific advisory board and travel compensation from Amylyx. **MEP** reports research grants from Dexcom and Recordati, consulting fees from MBX, Spruce, Recordati, Premier, Cello, Alpha sight, Boxer Capital, and Amylyx, scientific advisory board compensation from Amylyx and fees for participation as a DSMB member from Fractyl. **SB, JH, MG, RN, KF, JT,** and **ZY** are or were full-time employees of and may have stock option ownership in Amylyx Pharmaceuticals, Inc. **CC** reports consulting fees, license/APA compensation, and scientific advisory board compensation from Amylyx.

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