Reduction in Rate of Hypoglycemic Events with Avexitide in Post-Bariatric Hypoglycemia: Results from the Phase 2 and 2B Studies

Colleen Craig, MD[1*]; Tracey McLaughlin, MD, MS[1*]; Zhengyu Yang, PhD[2*]; Kelly Fox, MD[2*]; Ryan Miller, MD[2*]; Helen Margaret Lawler, MD[3*]; Dawn Belt Davis, MD, PhD[4*]; Marilyn Tan, MD, FACE[1*]

[1]Stanford University School of Medicine, Department of Medicine, Stanford, California, USA; [2]Amylyx Pharmaceuticals, Inc., Cambridge, Massachusetts, USA; [3]University of Colorado School of Medicine, Division of Endocrinology, Metabolism, and Diabetes, Department of Medicine, Aurora, Colorado, USA. [4]University of Wisconsin, Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Madison, Wisconsin, USA. *Potential conflict of interest may exist. Refer to the Disclosures section.

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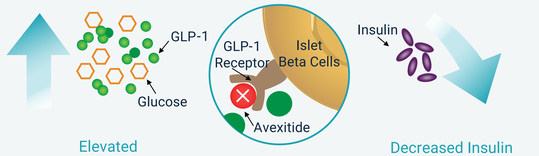
BACKGROUND

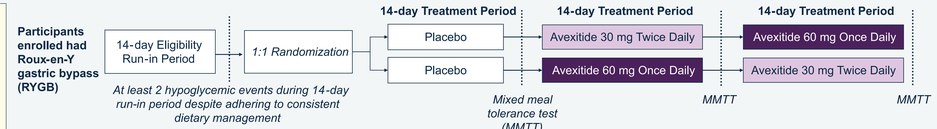
- Post-bariatric hypoglycemia (PBH) is a chronic condition characterized by hyperinsulinemic hypoglycemia that develops in some individuals who have undergone bariatric surgery[1-6]
- PBH is believed to be caused by changes in hormonal and glycemic patterns, including an excessive glucagon-like peptide-1 (GLP-1) response, as a result of altered nutrient transit post-surgery[1-4]
- PBH can cause debilitating hypoglycemic events associated with neuroglycopenia, including impaired cognition, poor coordination, loss of consciousness, and seizures which can result in a high degree of disability and major disruptions to independent living[5]
- Avexitide is an investigational, first-in-class glucagon-like peptide-1 (GLP-1) receptor antagonist designed to block the effect of excessive GLP-1, targeting a central pathway of PBH pathophysiology to mitigate hypoglycemia by decreasing insulin secretion and stabilizing glucose levels[1-4]
- To date, one Phase 2 randomized, multi-center, placebo-controlled crossover study (PREVENT trial) has been conducted to evaluate the efficacy and safety of avexitide for the treatment of PBH[6]
- In addition, 8 investigator-initiated studies (including a Phase 2b study) have been performed that together demonstrated the effects of avexitide treatment on reducing hypoglycemia in individuals with PBH and those with hyperinsulinemic hypoglycemia following other, non-bariatric gastrointestinal surgeries (e.g., gastrectomy)[3,7-13]

PROPOSED AVEXITIDE MECHANISM OF ACTION



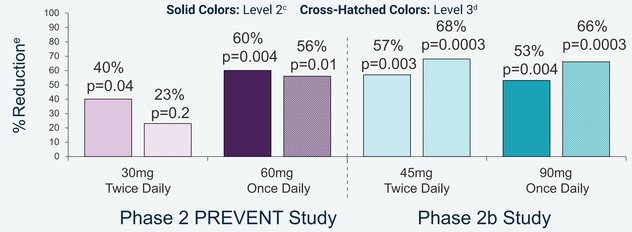
AVEXITIDE (AVX) PHASE 2[6] & 2b[7] CLINICAL TRIAL DESIGNS AND SELECT RESULTS

PHASE 2 PREVENT TRIAL DESIGN – 28-day, placebo-controlled crossover randomized, trial (N = 18[a])



PHASE 2 PHASE 2B TRIAL DESIGN – 28-day, open-label, investigator-initiated, crossover trial (N = 17[a])

% Reduction in Rate[b] of Hypoglycemia by Avexitide Dose



- Avexitide demonstrated statistically significant reductions in hypoglycemic events in Phase 2 and 2b clinical trials
- No clinically relevant increases were observed in fasting or peak postprandial plasma glucose levels
- Adverse events have generally been mild to moderate and transient with no treatment-related serious adverse events and no adverse events necessitating drug discontinuation

[a]*One excluded from the efficacy analysis due to major protocol deviation*
[b]*Rate defined as number of episodes in each treatment period normalized to 14 days*
[c]*Level 2 hypoglycemia: self-monitoring of blood glucose <54 mg/dL*
[d]*Level 3 hypoglycemia: a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery whether an individual receives external assistance or not*
[e]*Compared to placebo in Phase 2 and run-in in Phase 2b*

OBJECTIVE

Given that the phase 3 LUCIDITY trial will further evaluate avexitide in PBH with a primary efficacy outcome of composite reduction of Level 2 and 3 hypoglycemic events, the goal in this exploratory analysis is to understand the composite reduction of Level 2 and 3 hypoglycemic events in prior Phase 2 trials of avexitide in PBH

METHODS

- For each avexitide dose, the rate of composite Level 2 and 3 events[c,d] was calculated as the weekly number of discrete events during the respective treatment periods of the Phase 2 and 2b clinical trials
  - A negative binomial regression model was used, and a least-squares (LS) mean rate ratio (RR) vs placebo (for the Phase 2) and run-in (for the Phase 2b) of hypoglycemia during the treatment period was calculated
  - For the Phase 2b, the model included treatment, treatment sequence, and surgery type stratum as fixed effect, event rate in run-in period as covariate, and offset by duration of treatment period

RESULTS

FIGURE 1. AVX Significantly Reduced Rates of Composite Level 2&3 Hypoglycemia

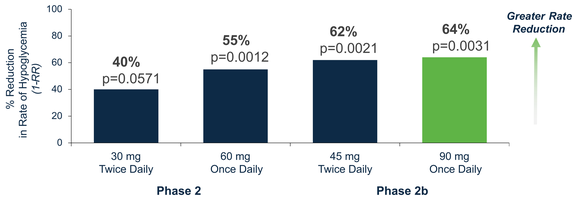


TABLE 1. Reduced Rates of Composite Level 2 and 3 Hypoglycemia in Phase 2

	Run-In Period n=17	Placebo n=17	Avexitide 30 mg Twice Daily n=17	Avexitide 60 mg Once Daily n=17
Composite Weekly Rate of Level 2&3 Hypoglycemia				
Mean (SD)	1.37 (1.244)	1.47 (1.049)	0.89 (1.101)	0.66 (0.609)
Median	1.04	1.50	0.50	0.50
Rate Ratio *(over placebo of hypoglycemia during treatment period)*				
LS Mean (SE)	N/A	N/A	0.60 (0.260)	0.45 (0.233)
95% CI	N/A	N/A	0.357, 1.016	0.281, 0.717
P-Value	N/A	N/A	0.0571	0.0012

Table 2. Reduced Rates of Composite Level 2 and 3 Hypoglycemia in Phase 2B

	Run-In Period n=16	Avexitide 45 mg Twice Daily n=16	Avexitide 90 mg Once Daily n=16
Composite Weekly Rate of Level 2&3 Hypoglycemia			
Mean (SD)	1.39 (1.908)	0.51 (0.719)	0.59 (1.604)
Median	0.93	0.25	0
Rate Ratio *(over run-in of hypoglycemia during treatment period)*			
LS Mean (SE)	N/A	0.38 (0.298)	0.36 (0.325)
95% CI	N/A	0.206, 0.687	0.187, 0.694
P-Value	N/A	0.0021	0.0031

Abbreviations: CI, confidence interval; SD, standard deviation; SE, standard error

CONCLUSIONS

- Avexitide significantly reduced rates of composite Level 2 and 3 hypoglycemia in its Phase 2 and 2b trials
- The 90 mg once daily dose, which is being further evaluated in the Phase 3 LUCIDITY trial, led to a 64% reduction in the composite rate of Level 2 and 3 events (p=0.0031)
  - With 90 mg once daily, mean and median number of events per week were 0.59 and 0, respectively, vs 1.39 and 0.93 during the run-in period
- The Phase 3 LUCIDITY trial is currently recruiting in the United States with topline data anticipated in 1H 2026

lucidity

SCAN TO LEARN MORE ABOUT THE PHASE 3 LUCIDITY TRIAL

CONTACT INFO: KELLY FOX, MD
Kelly_Fox@amylyx.com

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

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Disclosures

CC reports consulting fees, license/APA compensation, and compensation (including travel-related) for participation in a scientific advisory board from Amylyx. **ZY, KF,** and **RM** are or were full-time employees of and may have stock option ownership in Amylyx Pharmaceuticals, Inc. TM reports consulting fees from Amylyx, patents licensed to Amylyx, and compensation (including travel-related) for participation in a scientific advisory board from Amylyx. **HML** reports compensation (including travel-related) for participation in a scientific advisory board from Amylyx and reports consulting fees from Vogenx. DBD reports compensation (including travel-related) for participation in a scientific advisory board from Amylyx and reports reimbursement of travel from Recordati. **MT** reports consulting fees and scientific advisory board and travel compensation from Amylyx.

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