Efficacy and Safety of Avexitide for Treatment of Hypoglycemia after Gastrointestinal Surgery; Assessment of Novel Dosing Regimens in an Expanded Indication

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2022 ENDOCRINE SOCIETY

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Presenter Disclosures

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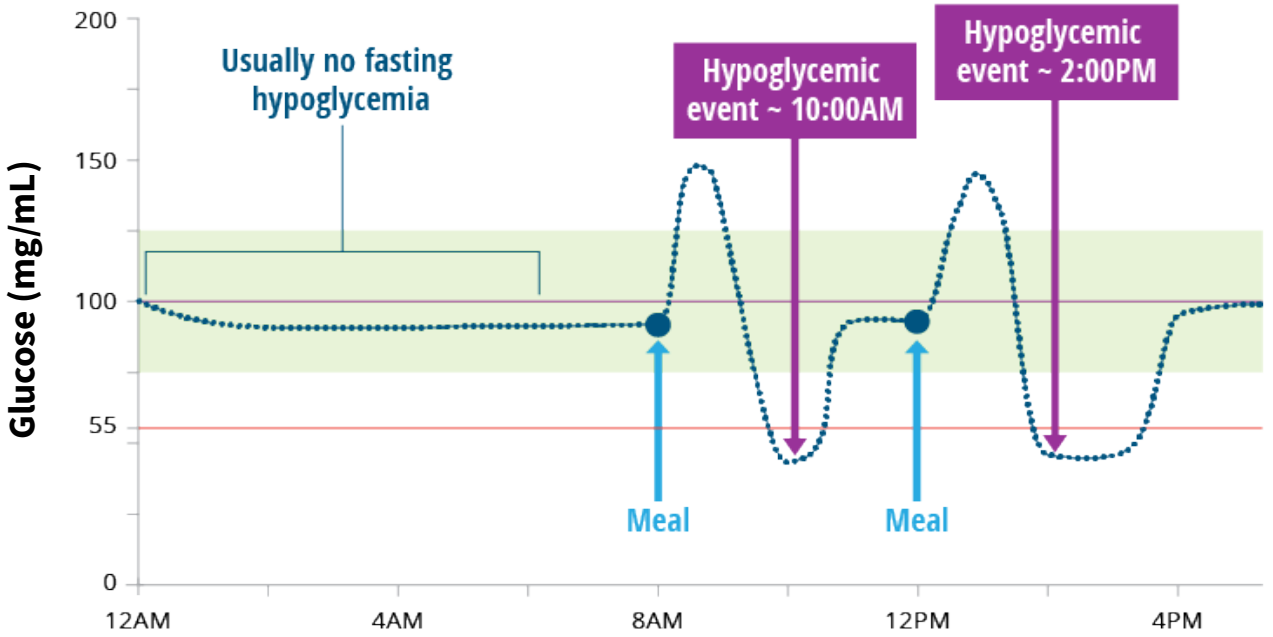
Post-Bariatric Hypoglycemia (PBH)

A COMPLICATION OF GASTROINTESTINAL SURGERY

- 29-34% after Roux-en-Y gastric bypass (RYGB)[1,2,3,4]
- 11%–23% after vertical sleeve gastrectomy (VSG)[1,2,3,4,5]; also reported after other GI surgeries
- Postprandial hypoglycemia 1-3 hours after meals
- Neuroglycopenic symptoms[1,2,5]
  - blurred vision, confusion, drowsiness, speech difficulty, incoordination, difficulty concentrating
- High frequency of hypoglycemia unawareness (37%)[5]
- Outcomes: seizures (59.4%)[5], LOC (50%)[5], hospitalization (50%)[5], MVA (9.4%)[5], death
- High degree of disability (93.8% consider themselves to be disabled)[5], inability to work (40.6%)[5], needing help with ADLs (9.4%)[5]



[1]Lee CJ et al. *Obesity*. **2015**; 23: 1079-1084
[2]Lee CJ et al.. *Surg Obes Relat Dis*. **2018**;14(6):797-802
[3]Papamargaritis D et al. *Obes Surg* **2012**;22:1600-1606
[4]Brix JM et al. *Obes Facts.* **2019;**12:397–406
[5]Craig CM et al. *Surg Obes Relat Dis*. **2021**;17(11):1865-1872

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Therapeutic Approach to PBH

NO APPROVED TREATMENTS; HIGH UNMET MEDICAL NEED

- **Medical nutrition therapy**
  - Frequent small meals/CHO restriction/low glycemic index
- **Stepped pharmacotherapy follows (off-label use)**
  - Acarbose → Octreotide → Diazoxide
  - Limited by efficacy/tolerability
  - Other off-label therapies: verapamil, diabetes medications
  - Glucagon
- **Surgical approaches for severe refractory cases**
  - Gastrostomy tube
  - RYGB reversal → weight regain; incomplete efficacy

SAFE, EFFECTIVE, AND TARGETED THERAPIES ARE URGENTLY NEEDED

Salehi et al, *J Clin Endocrinol Metab.* **2018**;103(8):2815-2826.

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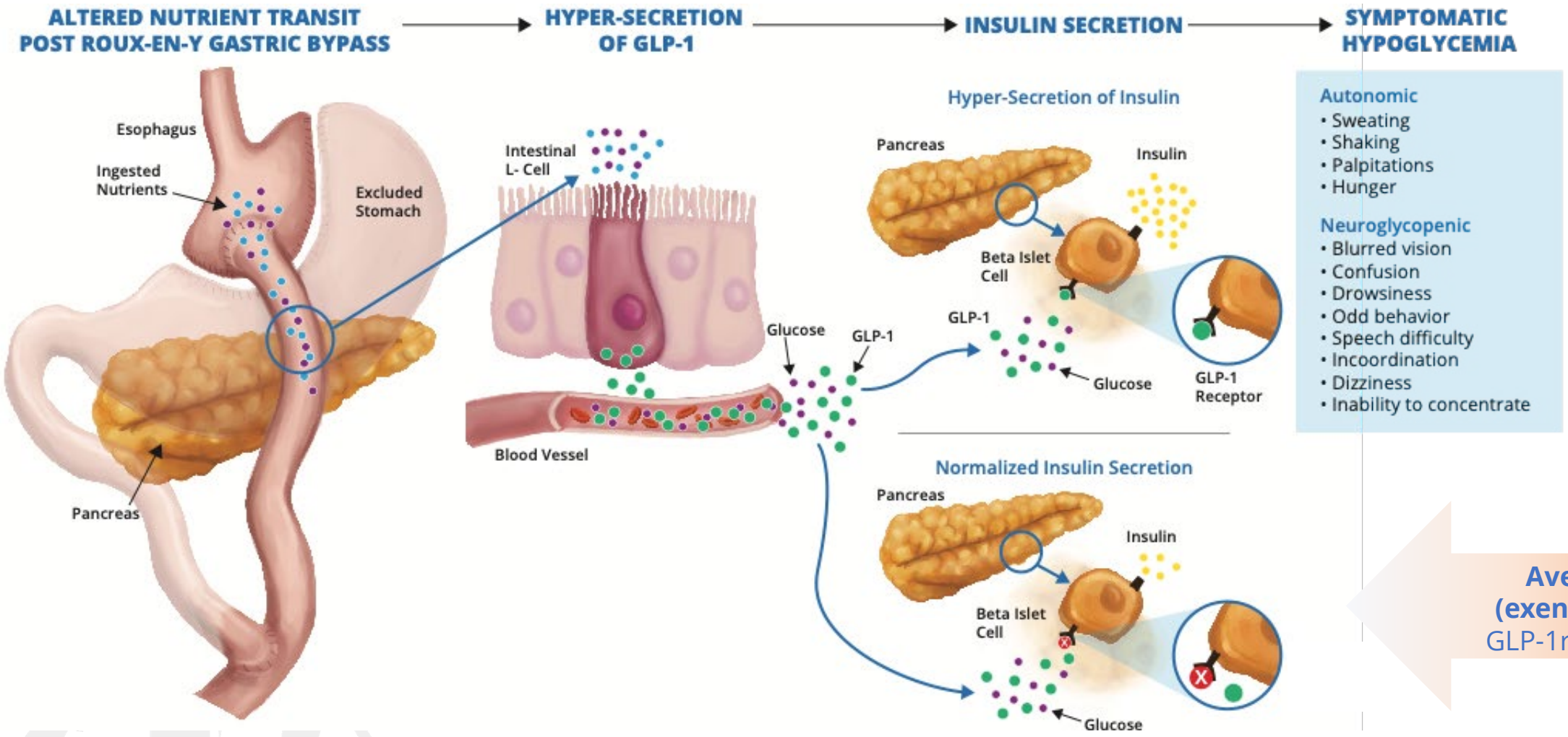
Pathophysiology: Exaggerated Secretion of GLP-1

CAUSING SYMPTOMATIC HYPERINSULINEMIC HYPOGLYCEMIA



Avexitide (exendin 9-39)
GLP-1r Blockade

Craig et al. *Diabetes, Obes and Metab.* **2018**;20(2):352-361.

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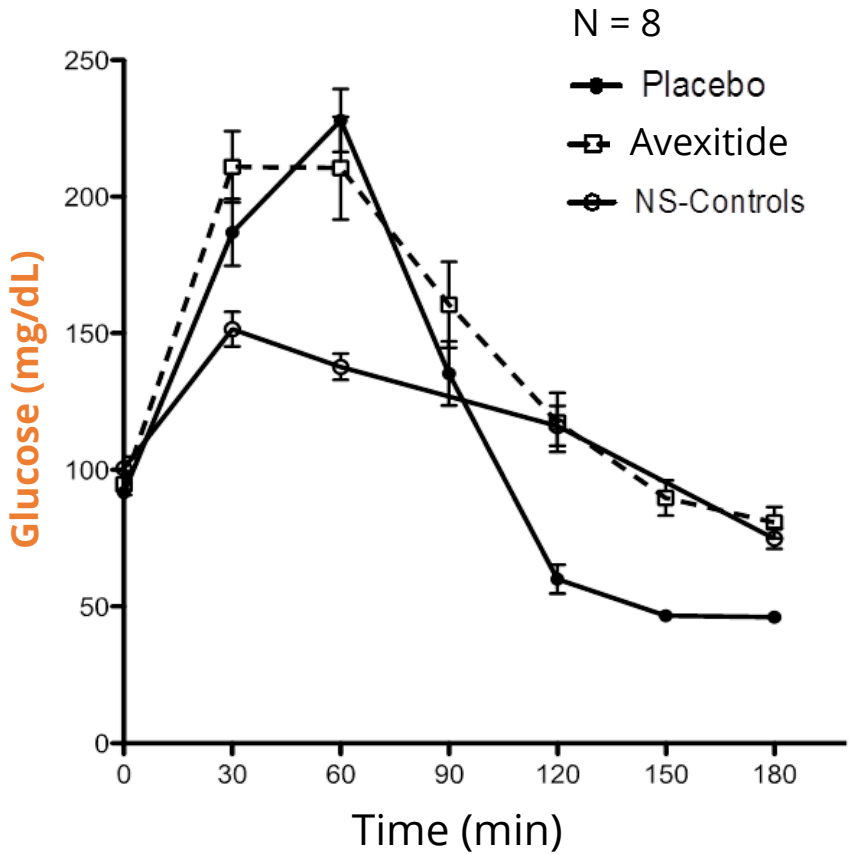
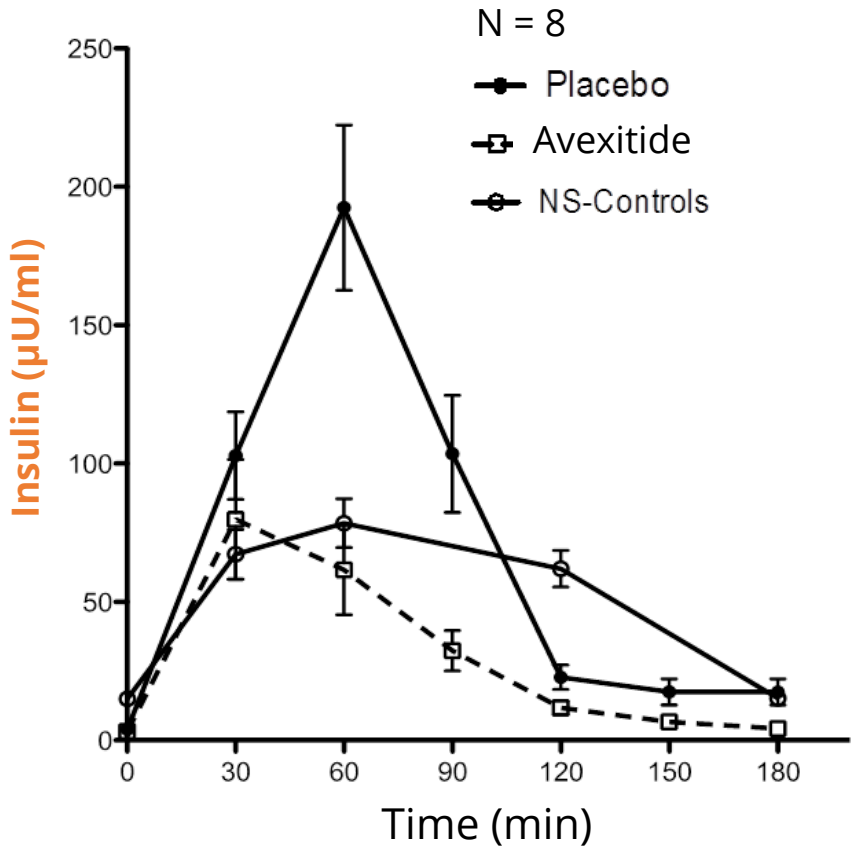
GLP-1 Receptor Antagonism: A Targeted Therapeutic Approach to PBH

PROOF OF CONCEPT STUDY DEMONSTRATED PREVENTION OF HYPERINSULINEMIC HYPOGLYCEMIA





NS-Controls = Non-surgical controls

Avexitide Infusion

- **100%** prevention of hypoglycemia
- Increased the plasma glucose nadir by 70%, matching NS controls
- Ameliorated hyperinsulinemia despite earlier and equally high peak plasma concentrations
- Did not alter fasting insulin or insulin clearance

Craig et al. *Diabetologia*, **2017**;60(3):531-540.

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Prior Avexitide Trials

SAFE AND EFFECTIVE PREVENTION OF HYPERINSULINEMIC HYPOGLYCEMIA IN PATIENTS WITH PBH

Study	# of Patients	Dosing/Duration	Status
IV Infusion	8	Single dose	Published in *Diabetologia*
SubQ Injection – SAD	8	Single dose	Presented at ADA 2016 | Published in *Diabetes, Obesity and Metabolism*
SubQ Injection – MAD	20	Up to 3 days BID	Presented at ADA 2017 | Published in *Diabetes, Obesity and Metabolism*
SubQ Injection - **PREVENT**	18	28 days QD/BID	Presented at ENDO 2019 | Published in *JCEM*

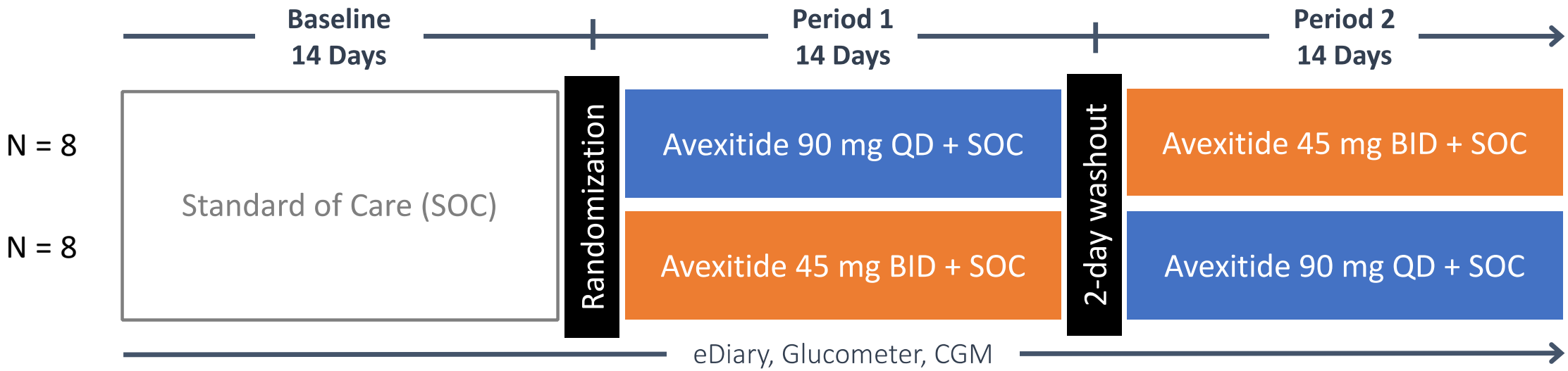
PREVENT Randomized, Placebo-controlled Crossover Trial of Avexitide for Treatment of PBH

- 18 patients with PBH: avexitide 30 mg BID x 14 days and 60 mg once daily x 14 days
- Avexitide raised glucose nadir by 21% (p=0.001) and 26% (p=0.0002), lowered insulin peak by 23% (p=0.029) and 21% (p=0.042)
- Significant reductions in rates of Levels 1, 2, and 3 hypoglycemia as captured by SMBG/e-Diary
- Significant reductions in hypoglycemia on blinded CGM without clinically relevant hyperglycemia
- PK/PD assessment suggested 45 mg BID or 90 mg daily dosing

Craig CM et al. *J Clin Endocrinol Metab*. **2021**;106(8):e3235-e3248.

Avexitide for Hypoglycemia after GI Surgery

DOSE EXPLORATION IN AN EXPANDED PATIENT POPULATION[1]



Primary efficacy endpoint

Rate of daytime Level 2 hypoglycemia by CGM (glucose <54 mg/dL)

[1]Enrollment Population: RYGB, VSG, esophagectomy, gastrectomy, Nissen fundoplication patients with severe, recurrent, diet-refractory hypoglycemia

[2]*Diabetes Care* **2019**;42(S1):S61–S70

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Participant Characteristics

16 PARTICIPANTS WITH SEVERE HH AFTER RYGB, VSG, GASTRECTOMY, NISSEN FUNDOPLICATION

Characteristic	Total (N=16*)
Demographic / Anthropomorphic Characteristic	
Sex, female/male, n (%)	14/2 (87.5/12.5)
Age, mean (SD), years	47.8 (12.8)
Weight, mean (SD), kg	79.4 (14.8)
BMI, mean (SD), kg/m^2	28.4 (5.2)
Surgical Subtype	
RYGB (%)	9 (56.2)
Nissen (%)	1 (6.2)
VSG (%)	4 (25.0)
Gastrectomy (%)	2 (12.5)
Clinical History	
History of type 2 DM before surgery, n (%)	0
Time since surgery, mean (SD), months	76.3 (51.1)
Time to first experience of postprandial hypoglycemia, mean (SD), months	15.4 (22.1)
History of LOC due to HH, n (%)	7 (43.7)
History of hospitalization due to HH, n (%)	1 (6.2)
History of pharmacotherapy for HH, n (%)	11 (68.7)
History of surgery for HH, n (%)	1 (6.2)

*1 enrolled participant was not included in evaluable population due to major protocol deviation

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Significant Reductions in Hypoglycemia Events by SMBG / eDiary

CONSISTENT IMPROVEMENTS OBSERVED WITH BOTH DOSING REGIMENS

Parameter Measured by eDiary and SMBG	Treatment Period (n=16)						
	Baseline	Avexitide 45 mg BID			Avexitide 90 mg QD		
	Mean (SD)	Mean (SD)	% Decrease from Baseline	*p*-value	Mean Event Rate (SD)	% Decrease from Baseline	*p*-value
Rate[1] of Level 1 Hypoglycemia[2]	5.9 (5.23)	2.7 (4.32)	53.8%	0.0028	1.9 (3.78)	67.5%	0.0005
Rate of Level 2 Hypoglycemia[3]	2.7 (3.10)	1.2 (1.42)	56.8%	0.0027	1.3 (3.72)	53.3%	0.0043
Rate of Level 3 Hypoglycemia[4]	2.5 (3.18)	0.8 (1.22)	67.5%	0.0003	0.9 (2.88)	66.1%	0.0003

[1] Rate is defined as number of episodes in each treatment period normalized to 14 days
[2] Level 1 Hypoglycemia is defined as SMBG concentrations <70 mg/dL
[3] Level 2 Hypoglycemia is defined as SMBG concentrations <54 mg/dL
[4] Level 3 Hypoglycemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery. This applies regardless of whether a patient receives external assistance.

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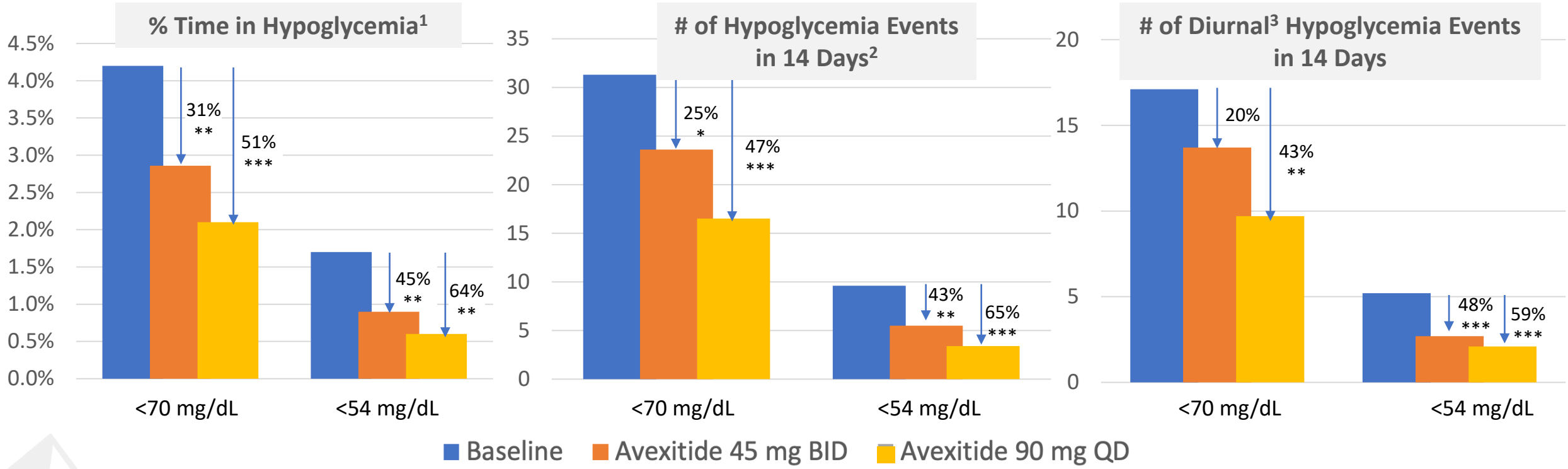
Significant Reductions in Hypoglycemia with Avexitide

% TIME IN HYPOGLYCEMIA AND # OF HYPOGLYCEMIA EVENTS AS MEASURED BY BLINDED CGM



[1] Percent Time in Hypoglycemia = total hours of CGM readings below 70 mg/L or 54 mg/dL divided by total CGM wear time
[2] Event Rate is defined as number of episodes below range (70 or 54 mg/dL) for at least 15 minutes during each treatment period normalized to 14 days
[3] Diurnal is defined as 8am-10pm

* $p<0.05$
** $p<0.01$
*** $p<0.001$

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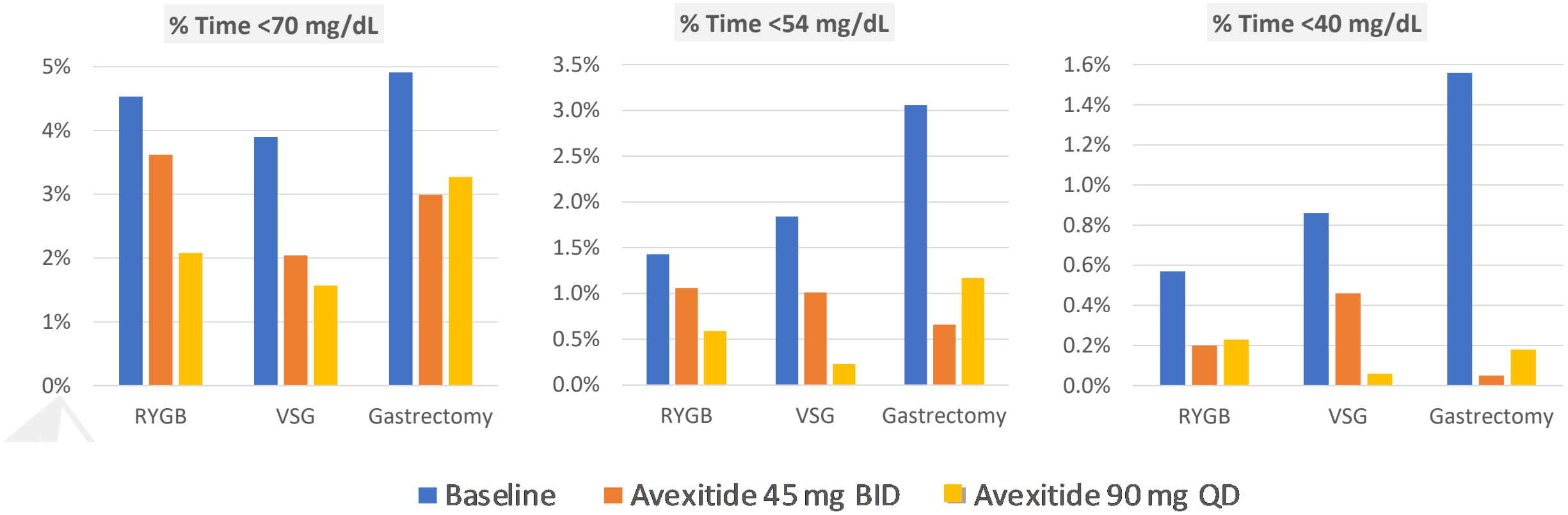
Significant Reductions in % Time in Hypoglycemia by CGM

AMPLIFICATION OF EFFECT FOR POST-GASTRECTOMY PATIENTS



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Avexitide Safety

AVEXITIDE WAS WELL-TOLERATED WITH NO SAFETY SIGNALS IDENTIFIED

- No SAEs
- Most common AEs: diarrhea, headache, bloating, and injection site reaction / bruising
- AEs were mild to moderate in severity and transient
- All AEs were self-limited and resolved without treatment
- No participant withdrawals

Conclusions

EFFICACY AND SAFETY SUPPORT NOVEL DOSING REGIMEN IN AN EXPANDED INDICATION

- Avexitide (exendin 9-39) is a first-in-class GLP-1 receptor antagonist in development for treatment of PBH and other forms of HH, including congenital hyperinsulinism
- 28 days of treatment in patients with HH after RYGB, VSG, gastrectomy, Nissen fundoplication demonstrated clinically meaningful improvements:
    - Significant reductions in the rates of Levels 1-3 hypoglycemia by SMBG and eDiary
    - Significant reductions in TBR and hypoglycemia events by CGM
- Benefits were seen across all surgical subtypes and with both dosing regimens
- Avexitide was well-tolerated, with no significant safety concerns observed in this study

Acknowledgements

AVEXITIDE STUDY TEAM

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Stanford University School of Medicine

Dalia Perelman, RD
Stanford University School of Medicine

Colleen Craig, MD
Eiger BioPharmaceuticals, Inc.

Tracey McLaughlin, MD, MS
Stanford University School of Medicine

STUDY PARTICIPANTS

“My husband noted I’m in a much better mood, and my nocturnal hypoglycemia was all gone.”

“Experience was amazing…”

"I felt great and normal after a very long time - very happy.”

“I’m back to practicing as a [professional] with full cognitive functioning.”

“Feeling protected, mood is much better, the explosive behavior has been much better.”

“Memory loss and recall improved.”

“I feel like myself again after a very long time.”

FUNDING