



Developing a Treatment for Post-Bariatric Hypoglycemia

December 9, 2016



Forward-Looking Statements

This presentation and the oral commentary contain “forward-looking” statements that involve substantial risks and uncertainties. All statements other than statements of historical facts, including statements regarding our future financial condition, timing for and outcomes of clinical results, business strategy and plans and objectives for future operations, are forward looking statements. These forward-looking statements include terminology such as “believe,” “will,” “may,” “estimate,” “continue,” “anticipate,” “contemplate,” “intend,” “target,” “project,” “should,” “plan,” “expect,” “predict,” “could,” “potentially” or the negative of these terms. Forward looking statements are our current statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our ongoing and planned clinical development, the timing of and our ability to initiate or enroll clinical trials, and our ability to make regulatory filings and obtain and maintain regulatory approvals for Sarasar, Bestatin, PEG IFN Lambda and our other product candidates, our intellectual property position, the potential safety, efficacy, reimbursement, convenience clinical and pharmaco-economic benefits of our product candidates, commercial opportunities, including potential market sizes and segments, our ability to commercialize, expectations regarding clinical trial data and FDA outcomes, our results of operations, cash needs, spending of the proceeds from this offering, financial condition, liquidity, prospects, growth and strategies, the industry in which we operate and the trends that may affect the industry or us.

Forward-looking statements involve known and unknown risks, uncertainties, assumptions and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. Forward-looking statements represent our beliefs and assumptions only as of the date of this presentation. Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons why actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

Agenda

<i>8:00 AM</i>	<i>Welcome</i> <ul style="list-style-type: none"><i>- Corporate Highlights and Pipeline</i><i>- HDV program update / next steps</i>	<i>David Cory</i>
<i>8:15 AM</i>	<i>PBH: Defining the Problem</i>	<i>Mary-Elizabeth Patti, MD</i> <i>Joslin Diabetes Center</i>
<i>8:30 AM</i>	<i>Pharmacologic Approaches to PBH</i>	<i>Marzieh Salehi, MD</i> <i>Cedars-Sinai</i>
<i>8:45 AM</i>	<i>Exendin 9-39 in PBH</i> <ul style="list-style-type: none"><i>- Review of IV / SC Data</i><i>- Interim Results of MAD Study</i><i>- Novel Liquid Formulation</i><i>- Next Steps</i>	<i>Colleen Craig, MD</i> <i>Stanford / Eiger</i>
<i>9:05 PM</i>	<i>Panel Discussion and Q&A</i>	<i>All</i>

Post-Bariatric Hypoglycemia (PBH): A Challenging Clinical Syndrome



Mary-Elizabeth Patti, MD

**Investigator and Adult Endocrinologist
Research Division**

Director, Hypoglycemia Clinic

Joslin Diabetes Center

Harvard Medical School

Post-Bariatric Hypoglycemia (PBH)

Complication of Bariatric Surgery

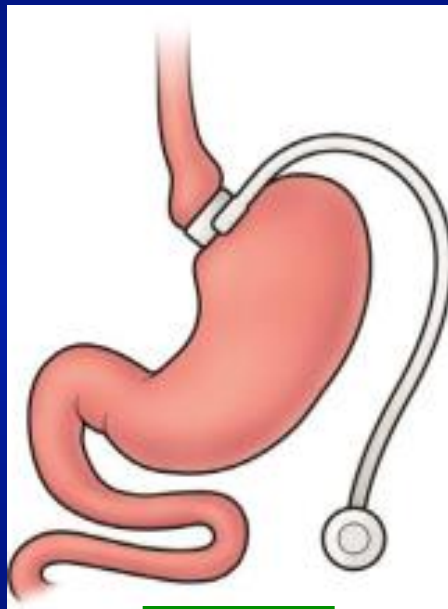
- **Bariatric surgery increasing worldwide**
 - 193,000 bariatric procedures in the US in 2015 and growing*
- **Post-prandial hyperinsulinemia and hypoglycemia**
 - Neuroglycopenia – seizures, loss of consciousness, and even death
 - Disability – impaired ability to work, drive, perform daily activities
 - Asymptomatic hypoglycemia is substantial
- **Impacts ~5-10% of gastric bypass patients: Orphan Disease**
 - ~ 60,000 gastric bypass procedures in US in 2015
 - ~ Up to 3,000 new patients annually in US (estimated incidence)**
 - ~ 30,000 current patients in US (estimated prevalence)**
- **No approved therapy; high unmet medical need**

Common Bariatric Procedures in US

Normal
Anatomy

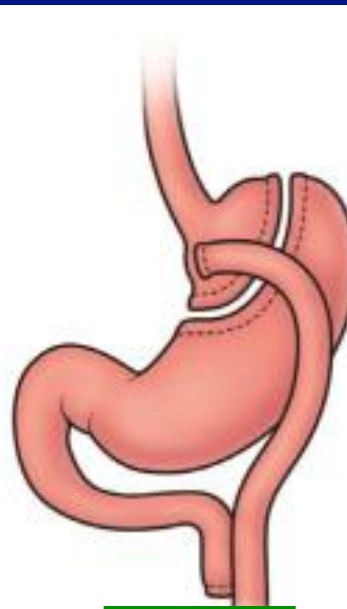


Adjustable
Gastric Band
(AGB)



10%

Roux-en-Y
Gastric Bypass
(RYGB)



27%

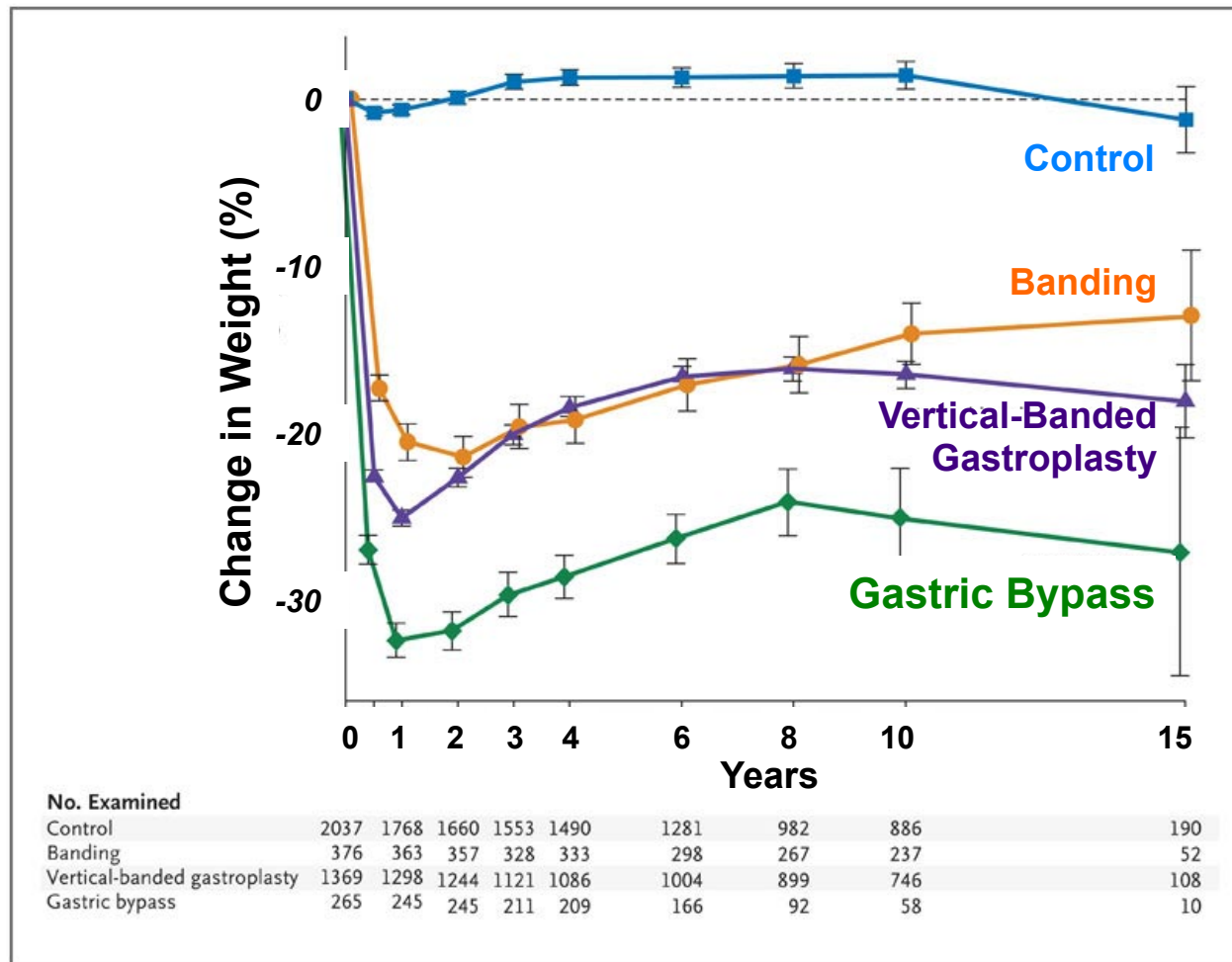
Vertical Sleeve
Gastrectomy
(VSG)



52%

ASMBS 2015: 193,000 procedures per year in US

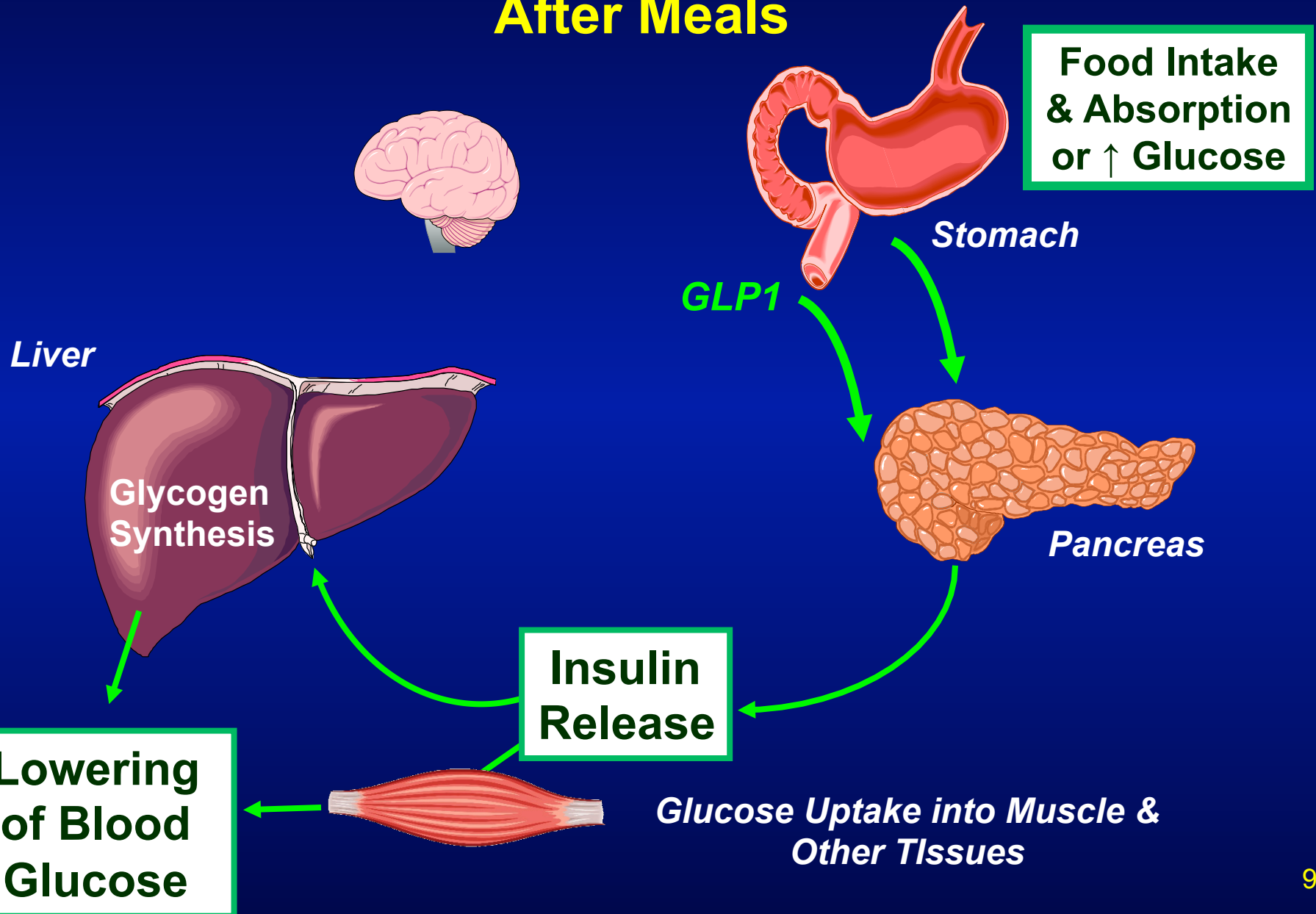
Gastric Bypass is Highly Effective for Sustained Weight Loss and Remission of Type 2 Diabetes



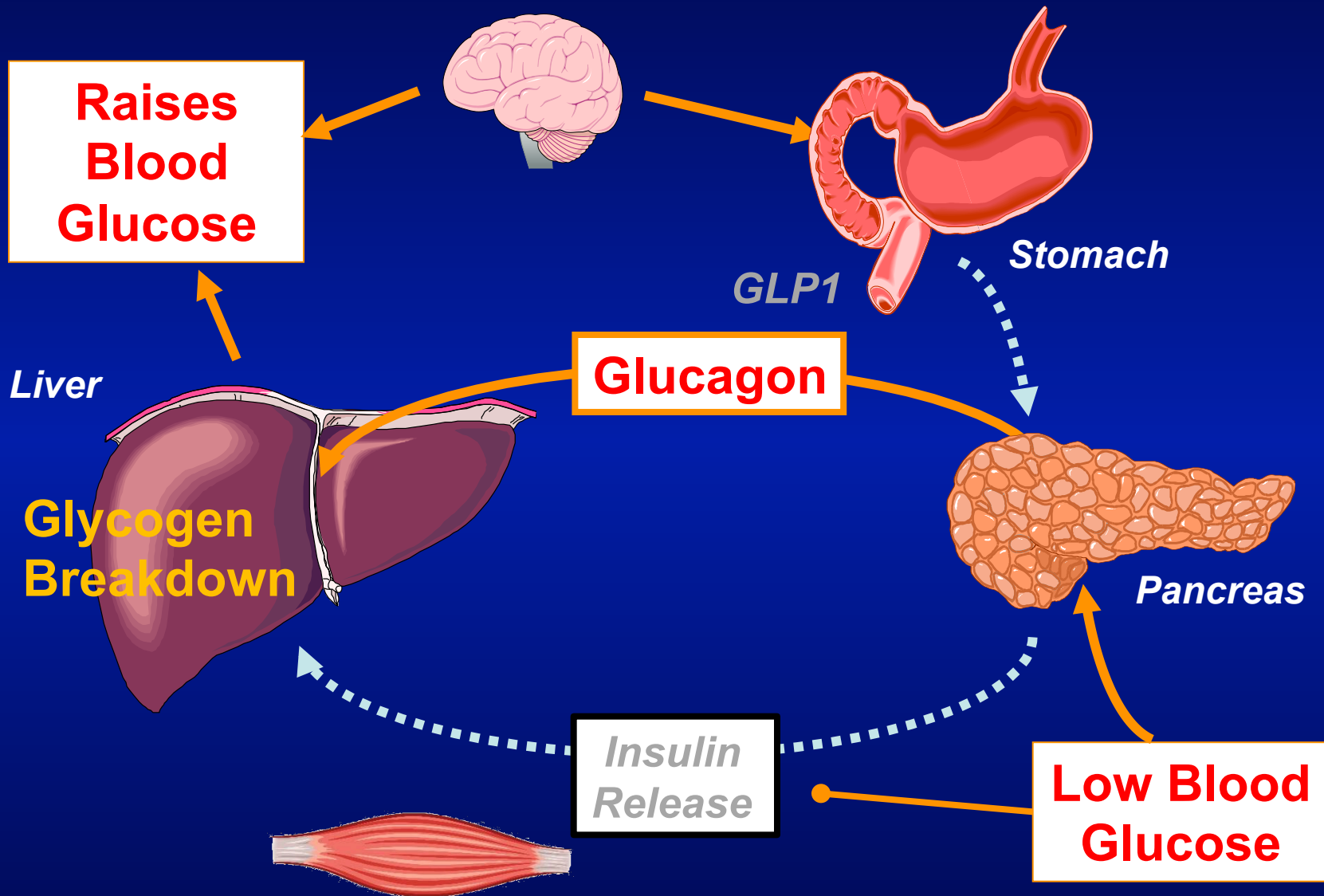
Blood Glucose Levels Are Tightly Regulated



Blood Glucose Levels Are Tightly Regulated After Meals



Blood Glucose Levels Are Tightly Regulated



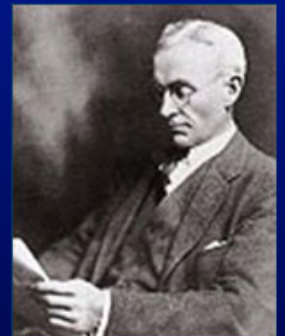
Counterregulatory hormones: cortisol, catecholamines, GH, neural input

How Do We Diagnose Hypoglycemia?

Whipple's triad required to diagnose hypoglycemia

- Symptoms of hypoglycemia
- Low plasma glucose at time of symptoms
($< 54 \text{ mg/dL}^*$)
- Relief of symptoms by raising glucose

*Allen O. Whipple
Surgeon*



Hypoglycemia Symptoms

Adrenergic

Tremor

Palpitations

Anxiety

Cholinergic

Sweating

Hunger

Paresthesias

Neuroglycopenia

Impaired cognition

Seizures

↓ Consciousness

- These symptoms are often nonspecific!
- Overlap with “dumping syndrome”
 - Occurring post-meals in bariatric patients

Hypoglycemia Symptoms

Adrenergic

Tremor

Palpitations

Anxiety

Cholinergic

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Hunger

Paresthesias

Neuroglycopenia

Impaired cognition

Seizures

↓ Consciousness

- Brain requires glucose for normal functioning
- Hypoglycemia Unawareness: A Threat to Safety
 - loss of adrenergic or cholinergic warning symptoms with repeated hypoglycemia
 - abrupt onset of neuroglycopenia
 - can result in serious falls, motor vehicle accidents, seizures, loss of consciousness



Post-Bariatric Hypoglycemia is Increasingly Recognized

- Mainly after gastric bypass, but also sleeve gastrectomy
- PBH can be mild, moderate or severe
- Mild / moderate can be managed with diet modification
 - Avoid easily digested carbohydrates (simple carbohydrates)
 - Focus on defined quantities of complex carbohydrates only
 - Frequent small meals
 - No liquids with meals
 - Snack before activity
 - Avoid alcohol
 - Carry glucose tablets at all times

Severe PBH

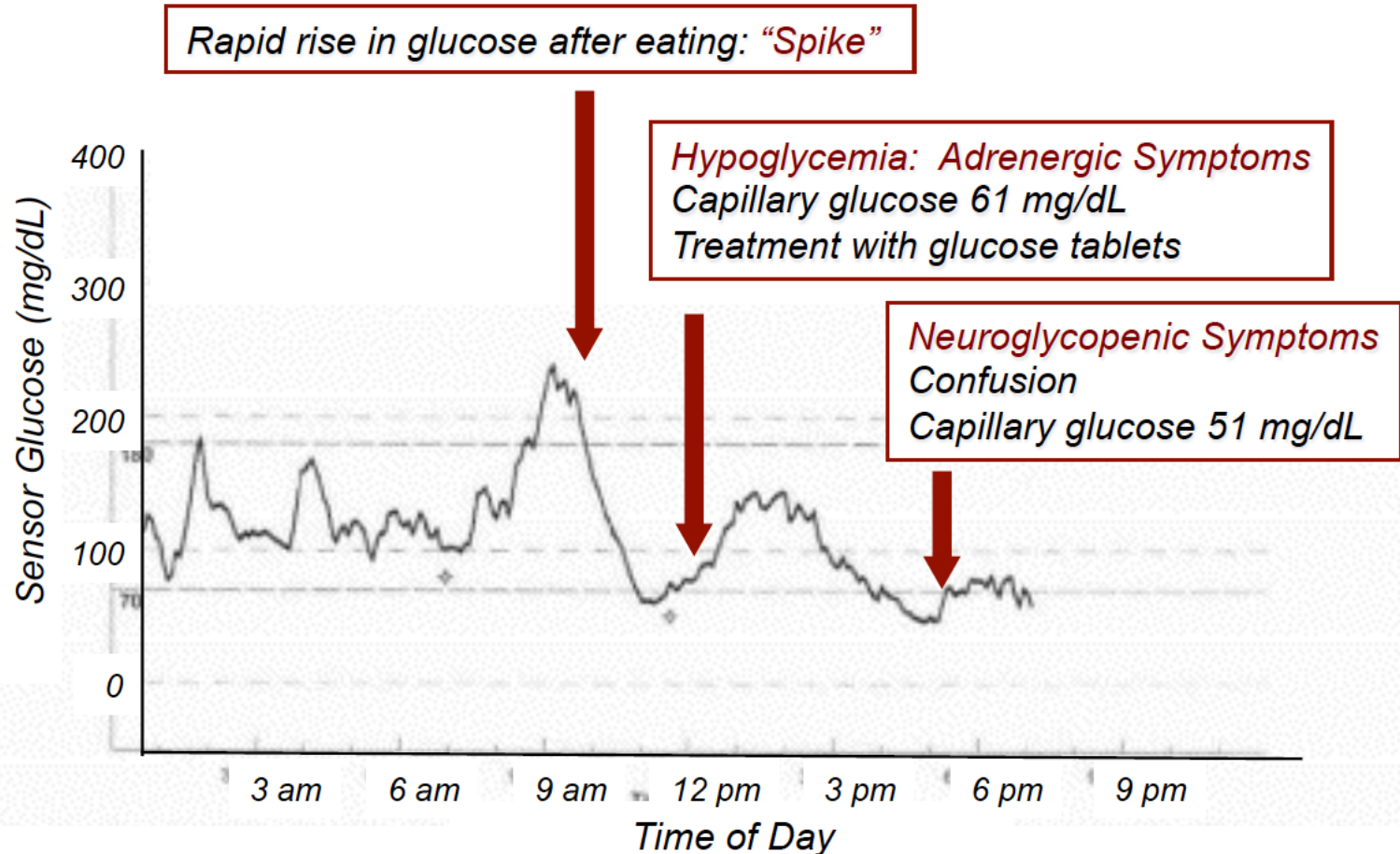
Occurs in a Subset of Patients

- Low plasma glucose levels at time of neuroglycopenia
 - with inappropriately high insulin levels
- Symptoms resolve with glucose administration
- Typical onset 2-3+ years after surgery
- Usually 1-3 hours after meals
- Normal glucose and insulin response to prolonged fasting
- Loss of consciousness, seizures, strokes, falls, disability
- Unresponsive to dietary management

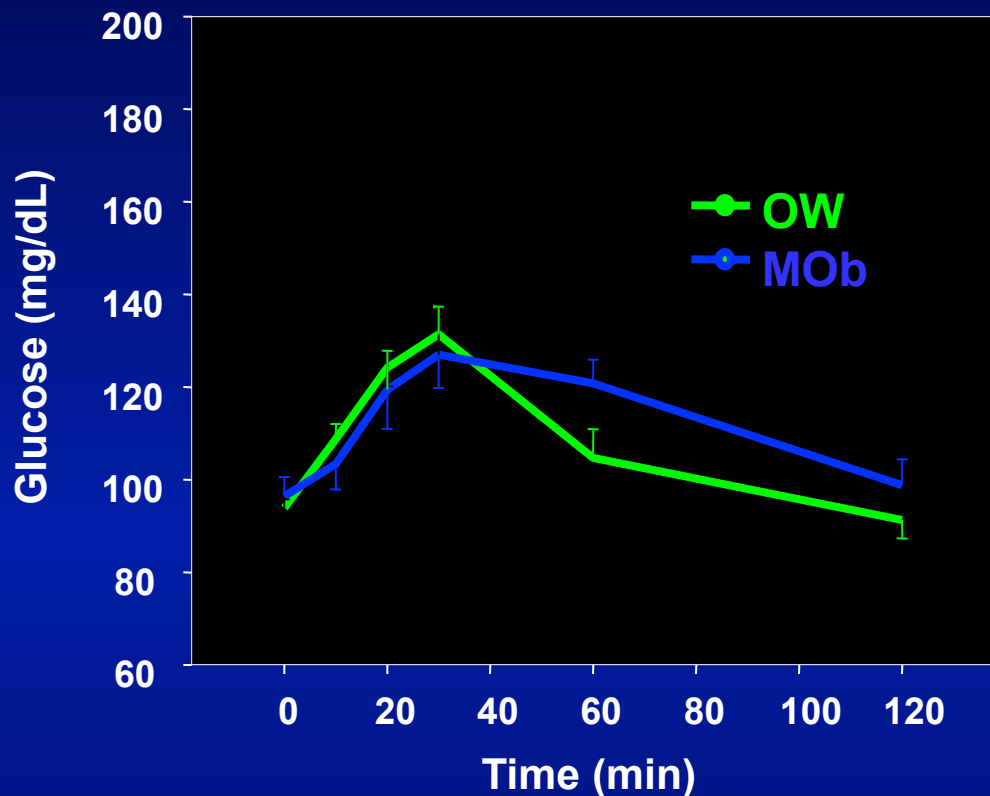
Roller Coaster of Post-Bypass Glycemia

Continuous Glucose Monitoring Reveals Spikes and Troughs

Patient Glucose Chart

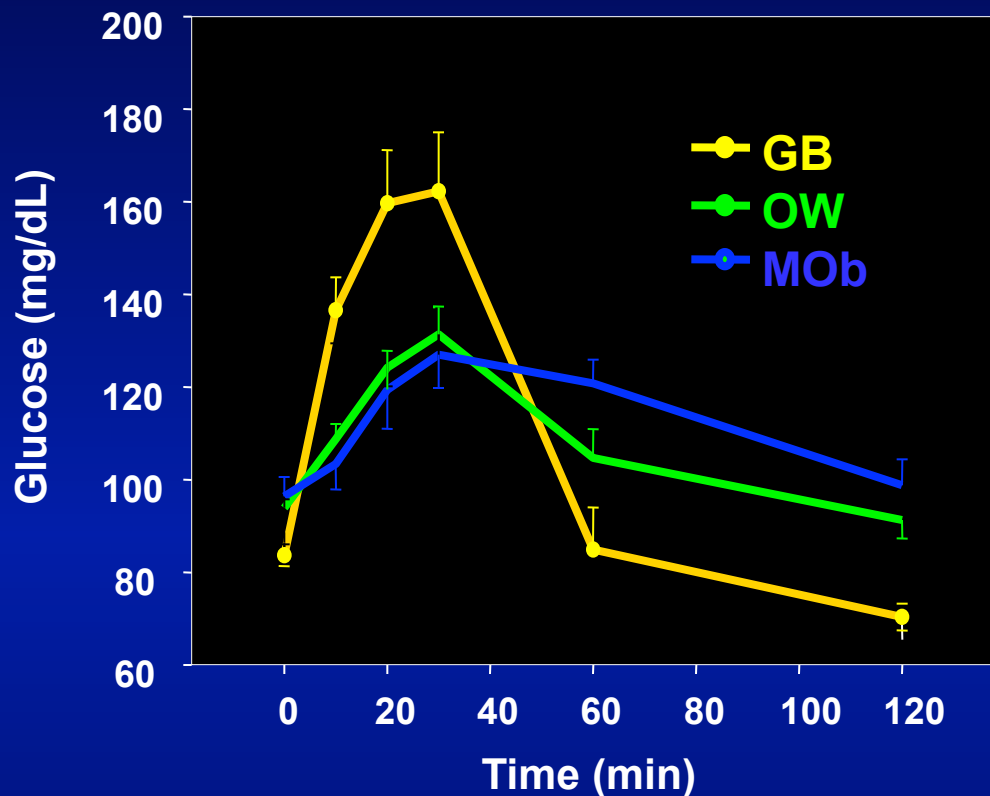


GB Alters Post-Prandial Glucose Patterns



- GB + NG** Post-bypass hypoglycemia patients with neuroglycopenia
- GB** Post-bypass, NO symptoms of hypoglycemia
- OW** Obese, matched to patients' current BMI
- MOb** Morbidly obese, matched to patients' pre-op BMI

GB Alters Post-Prandial Glucose Patterns



GB + NG

Post-bypass hypoglycemia patients with neuroglycopenia

GB

Post-bypass, NO symptoms of hypoglycemia

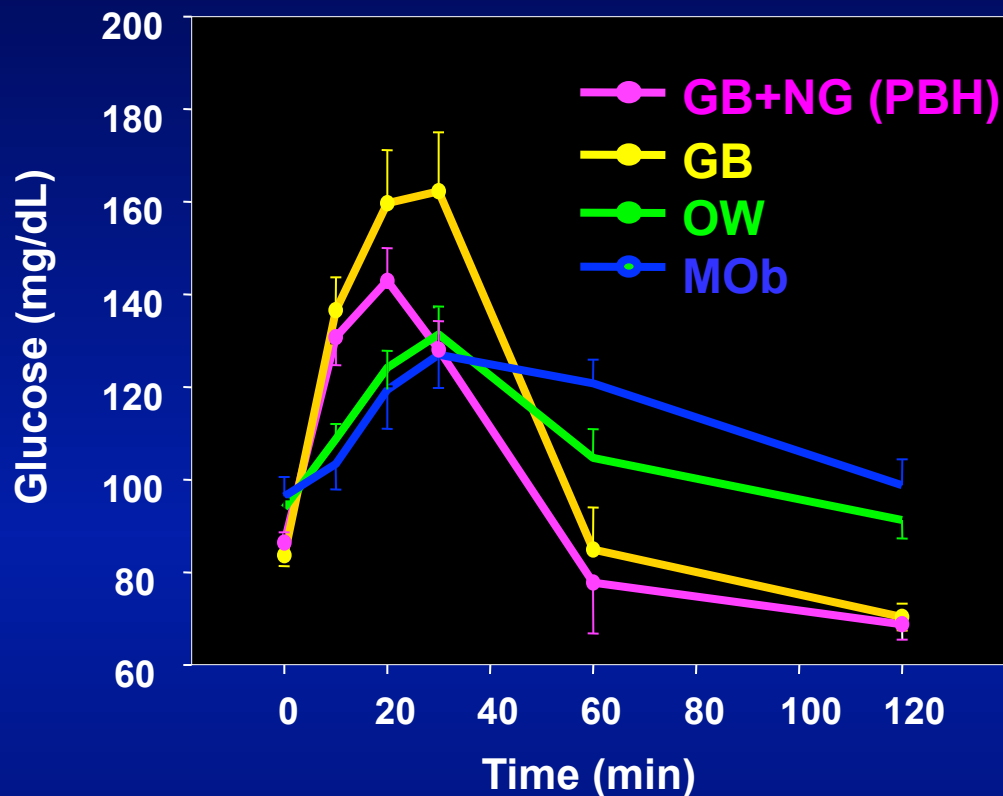
OW

Obese, matched to patients' current BMI

MOb

Morbidly obese, matched to patients' pre-op BMI

GB Alters Post-Prandial Glucose Patterns



GB + NG

Post-bypass hypoglycemia patients with neuroglycopenia

GB

Post-bypass, NO symptoms of hypoglycemia

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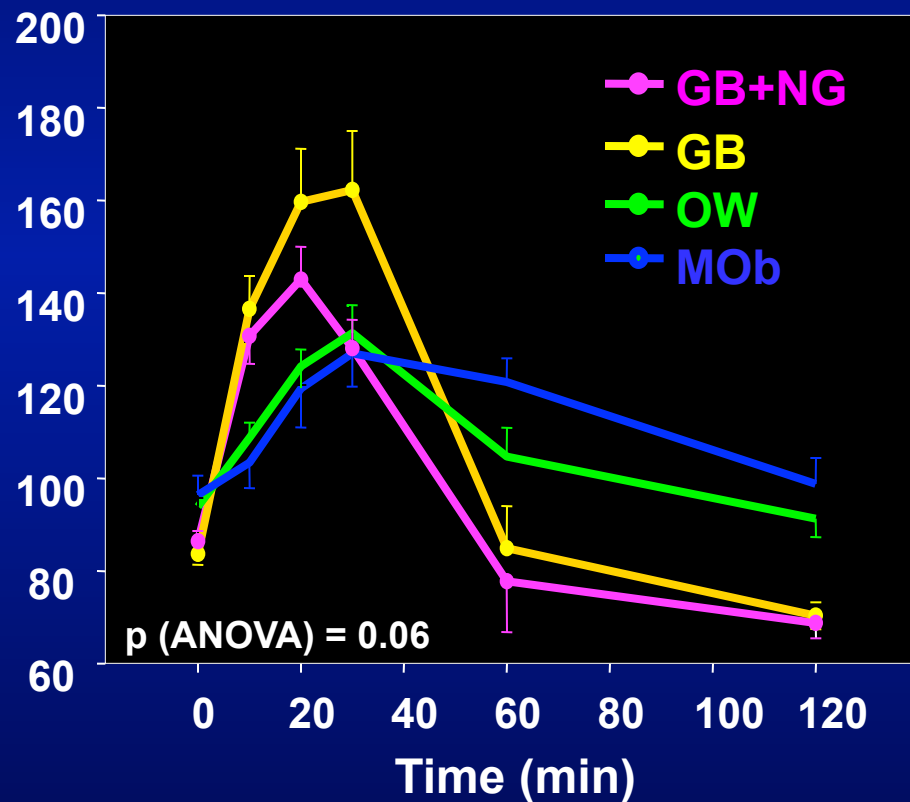
Obese, matched to patients' current BMI

MOb

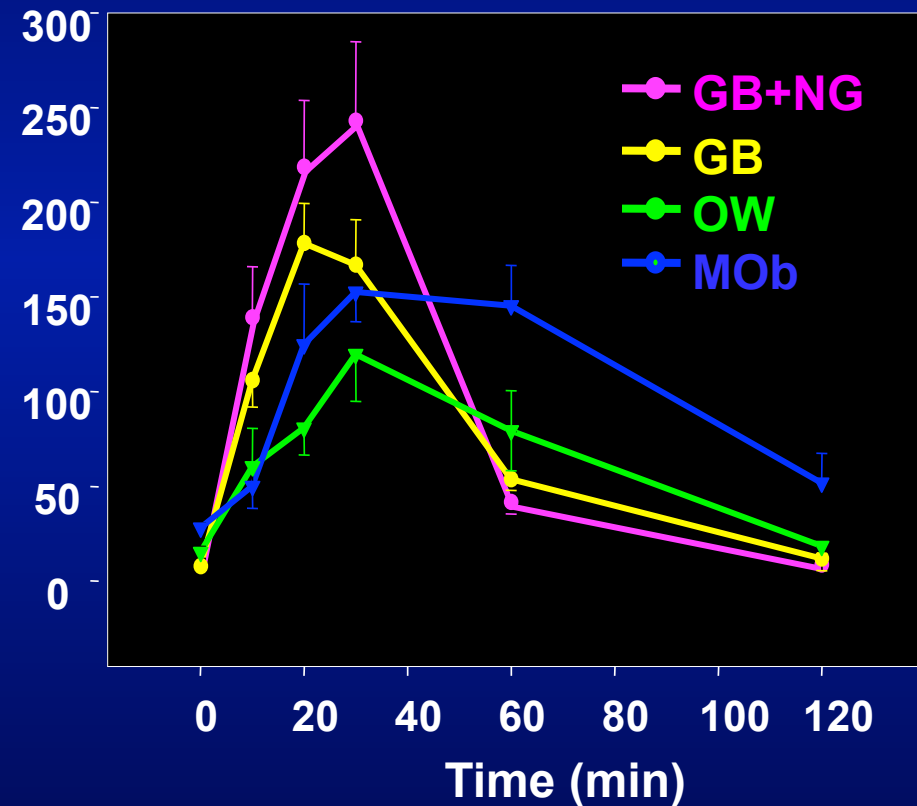
Morbidly obese, matched to patients' pre-op BMI

Higher Levels of Insulin In Post-GB Patients with Neuroglycopenia

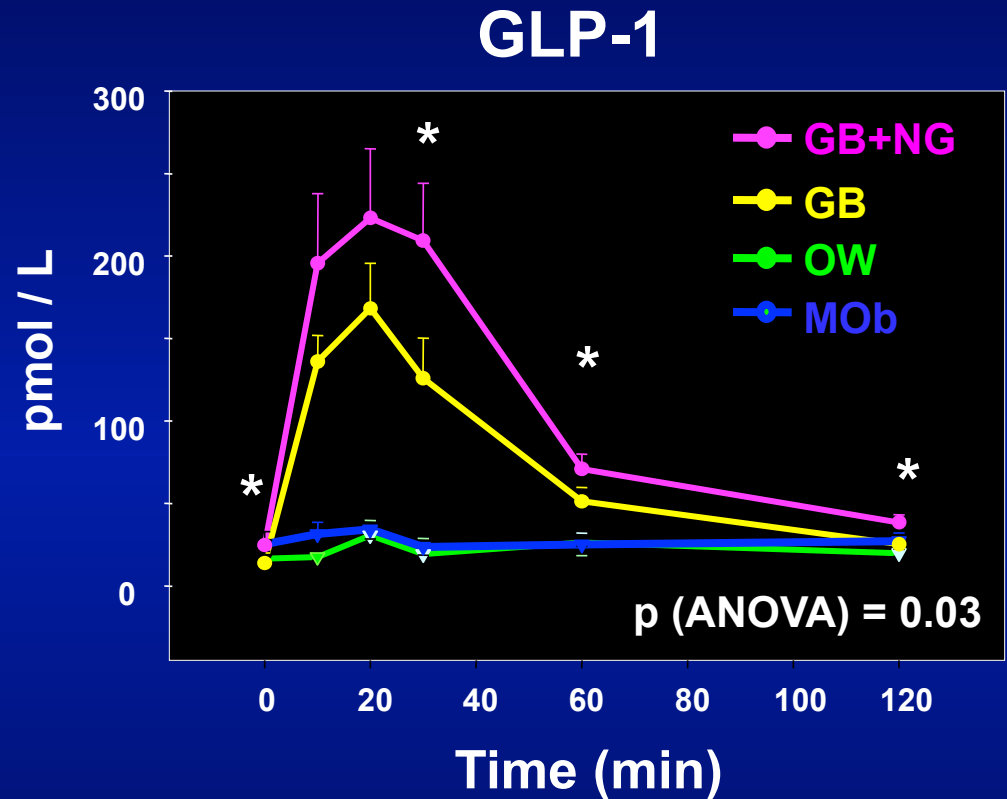
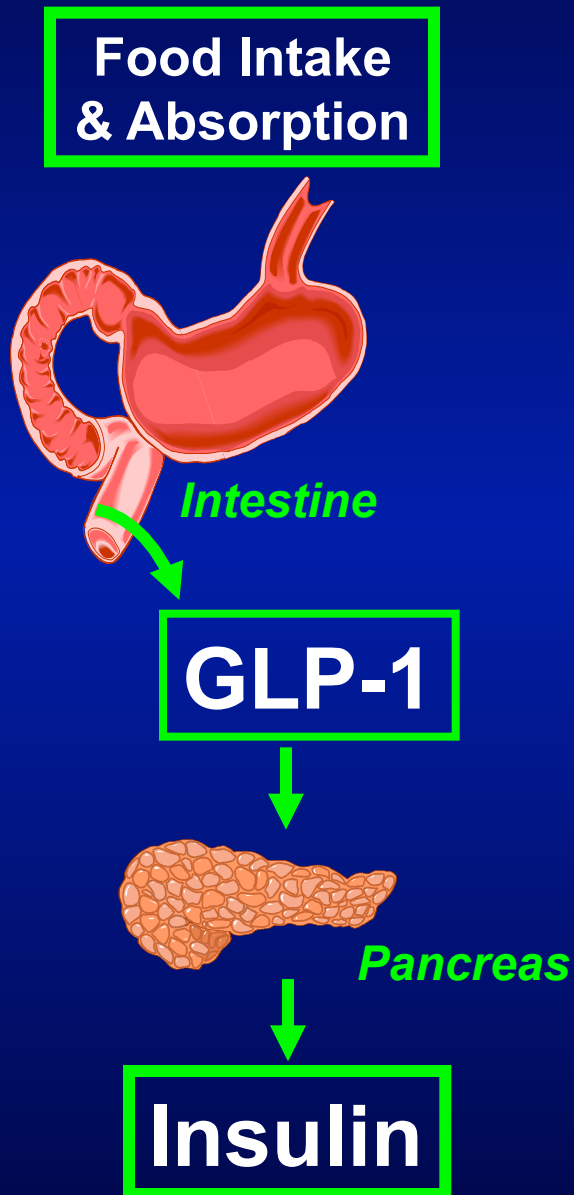
Glucose (mg/dL)



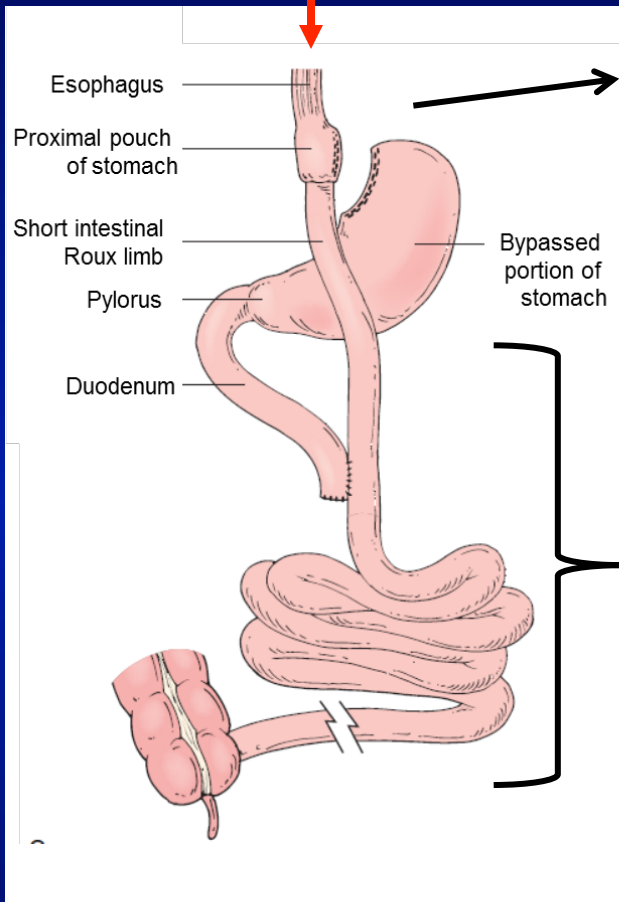
Insulin (μ U/mL)



GLP-1 Levels are Increased in PBH



Food Intake in Post-Bariatric Patient



- Accelerated Intestinal Delivery
- Rapid \uparrow Plasma Glucose

Chronic Intestinal & Neural Adaptation

- Dysregulated Enteroendocrine Cell Secretion
 - \uparrow Secretion of incretin hormones e.g. GLP-1
 - Altered Gut Microbiota
 - \uparrow Bile Acids
 - Altered Intestinal Metabolism
 - β -Cell Trophic Hormones
 - Insulin-independent glucose disposal

\uparrow Postprandial Insulin Secretion



Severe Hypoglycemia

Prevalence of PBH is Significant

Method of Diagnosis	Prevalence
Hospitalization	0.1 - 1% ^a
Clinical recognition	0.4 - 6.6% ^b
Symptoms (survey)	33% ^c
OGTT glucose < 50 mg/dL	10 - 33% ^d
MMTT glucose < 55 mg/dL	29% ^e
CGMS (sensor glucose < 55 mg/dL)	75% ^e
Duration	
CGMS (sensor glucose < 60 mg/dL)	30 - 71 min ^f

^aMarsk, Gribsholt, Sarwar, Lee; ^bKellogg, Gribsholt; ^cLee; ^dPigeyre, Goldfine, Papamargatis; ^eKefurt, ^fHalperin, Abrahamsson, Kefurt

PBH: A Debilitating Disorder

Summary

- **Bariatric surgery is now recommended in treatment guidelines as an option for obesity and type 2 diabetes***
- **RYGB and VSG are most common bariatric surgeries**
- **Post-prandial hyperinsulinemia and hypoglycemia**
 - **Impacts a significant % of RYGB patients**
 - **Neuroglycopenia, disability**
 - **Asymptomatic hypoglycemia is substantial**
- **Prevalence of post-bariatric hypoglycemia is significant**
- **Pharmacological treatment for PBH is needed**



Joslin

Allison Goldfine

Ping Li

Ali Bajwa

CRC Nurses & Staff

Christopher Mulla

Rohit Kulkarni

Susan Bonner-Weir

Gordon Weir

Franco Folli

Stefano La Rosa

Jonathan Dreyfuss

Hui Pan

Emmy Suhl

Joanne Rizzotto

Patients!

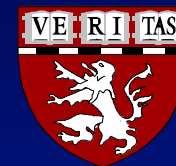
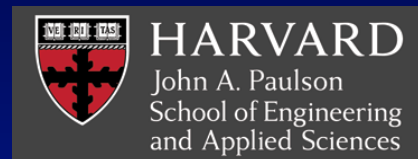
Thank you to...

**Harvard School
of Engineering**

Eyal Dassau

Alejandro Laguna

Frank Doyle



External Colleagues

Jens Holst

University of Copenhagen

Jean-Claude Reubi

University of Geneva

Clary Clish

Broad Institute

Pathology

Jeffrey Goldsmith

Eric Yee

Radiology

Elisa Franquet

Gerald Kolodny

George Watts



Surgery

Edward Mun

Daniel Jones

Ben Schneider

Douglas Hanto

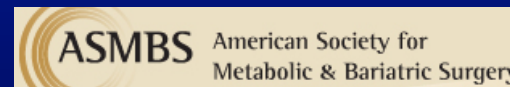
Mark Callery

David Lautz

Jim Moser

Funding

NIDDK-SBIR (with Xeris)



AZ/BMS/Amylin

Medimmune

Pharmacological Approaches to Hypoglycemia after Gastric Bypass Surgery

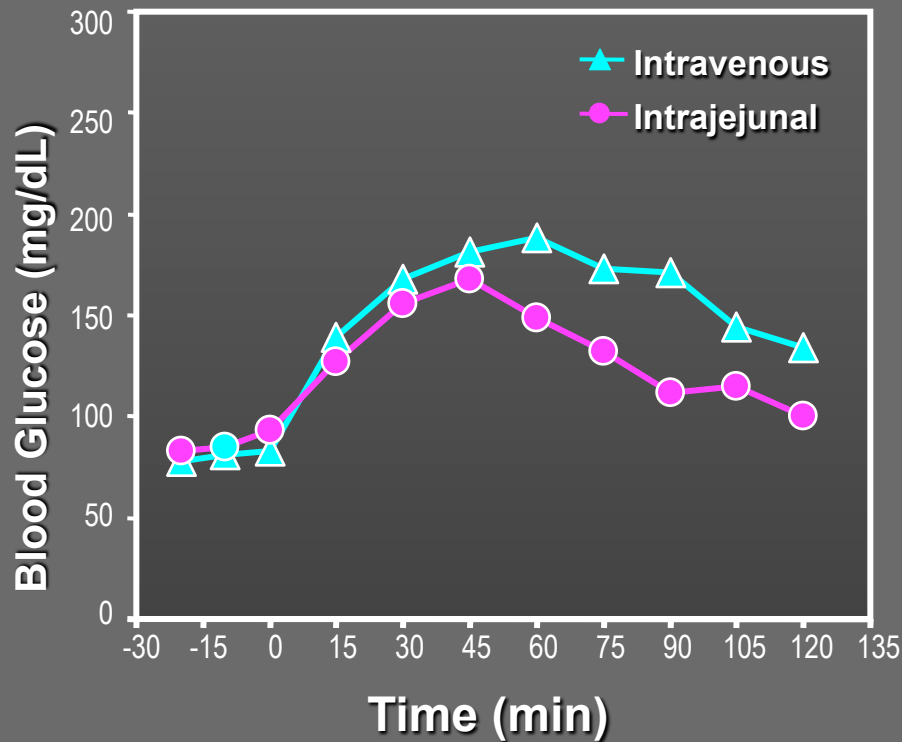


Marzieh Salehi, MD

*Director of the Clinical & Translational
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Cedars-Sinai Medical Center*

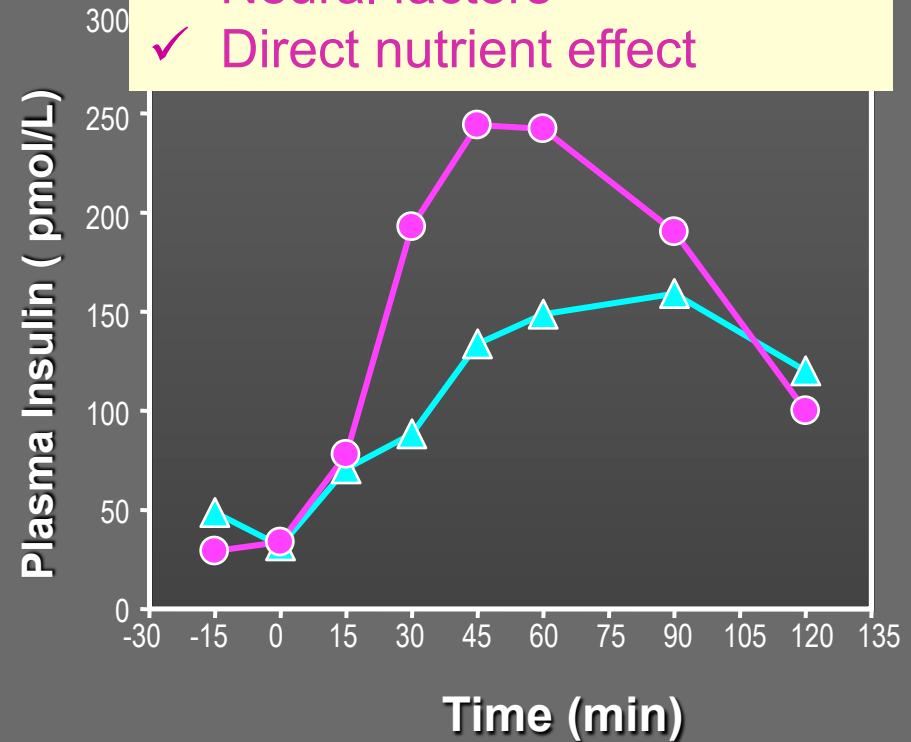
Insulin Secretion is Greater With Oral Compared to IV Glucose

Blood glucose

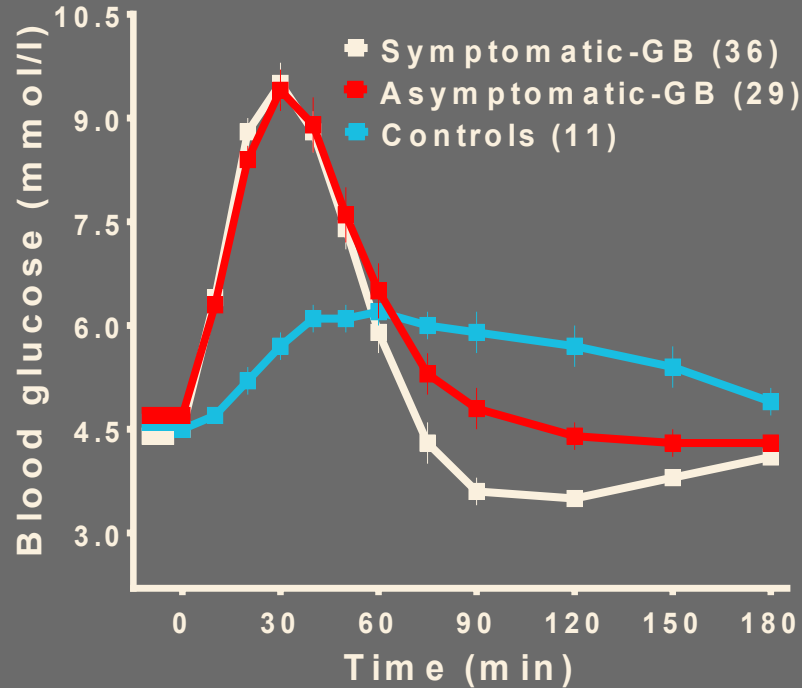


incretin effect

- ✓ GI hormones (GLP-1 / GIP)
- ✓ Neural factors
- ✓ Direct nutrient effect

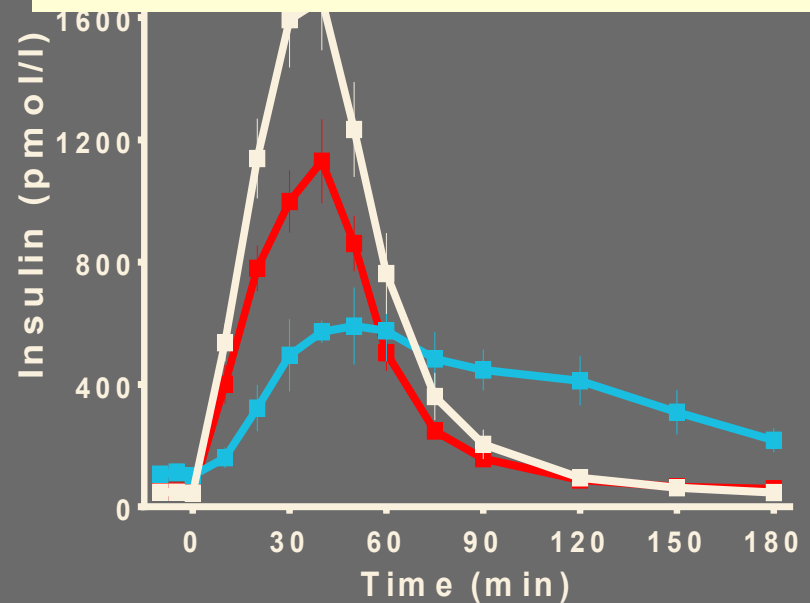


Postprandial insulin secretion after RYGB is exaggerated in post-RYGB hypoglycemia



Increased incretin effect after GB

- ✓ Gut hormones (mainly GLP-1)
- ✓ Neural factors
- ✓ Direct nutrient stimuli



Dietary Modification

First Line Intervention

- Frequent meals low in glycemic index
- Adding protein and fat to all meals and snacks
- Modification of source of carbohydrate - fructose instead of glucose
- Uncooked starch (Extend bar)
- Not effective in all patients with post-RYGB hypoglycemia
- Generally combined with other therapeutic options

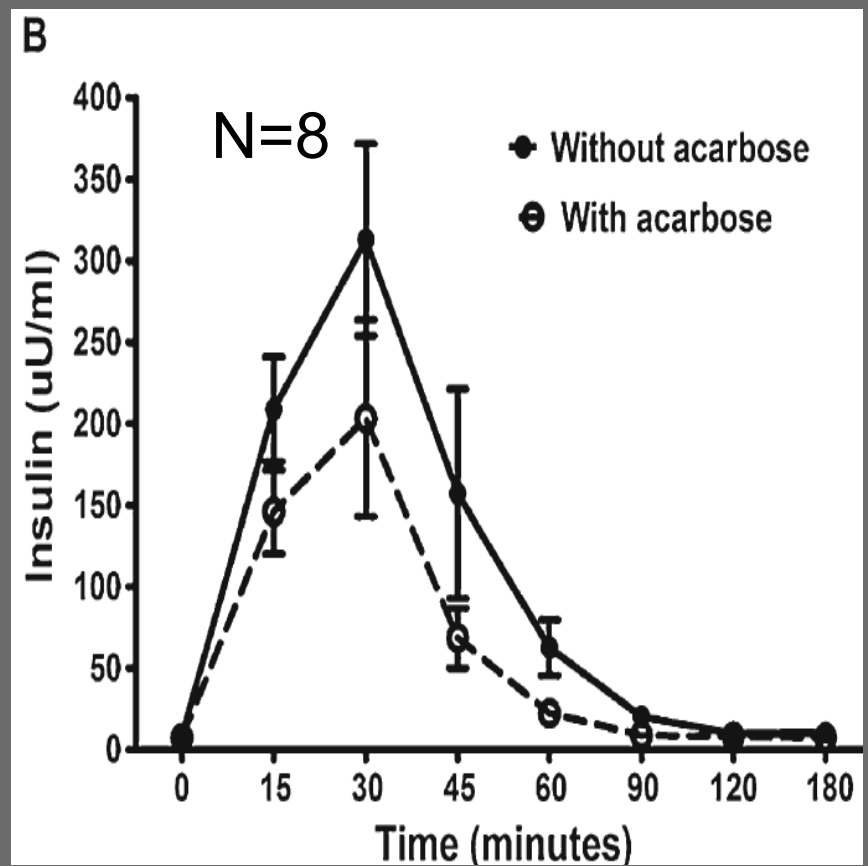
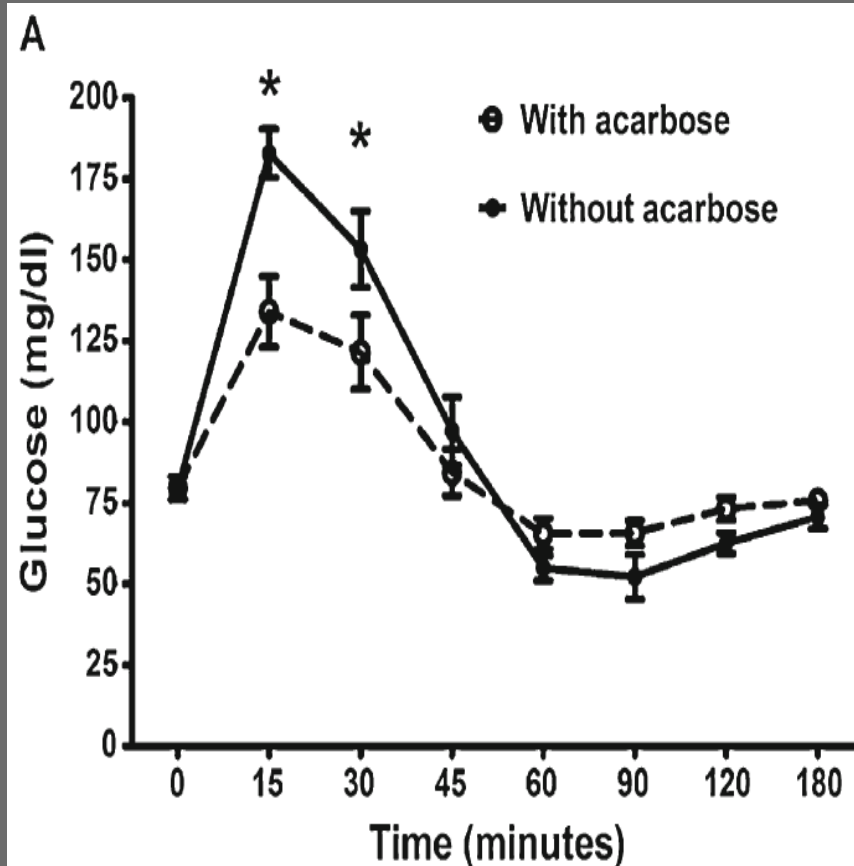
Pharmacological Approaches

No FDA Approved Rx

- Pharmacological Treatments (approved for other indications)
 - Acarbose
 - Somatostatin analogues
 - Diazoxide (symptom relief)
 - Calcium Channel Blockers (symptom relief)
 - GLP-1 receptor analogue (liraglutide)
- Investigational Pharmacological Treatments
 - XOMA 358
 - GLP-1 receptor antagonist (Exendin 9-39)

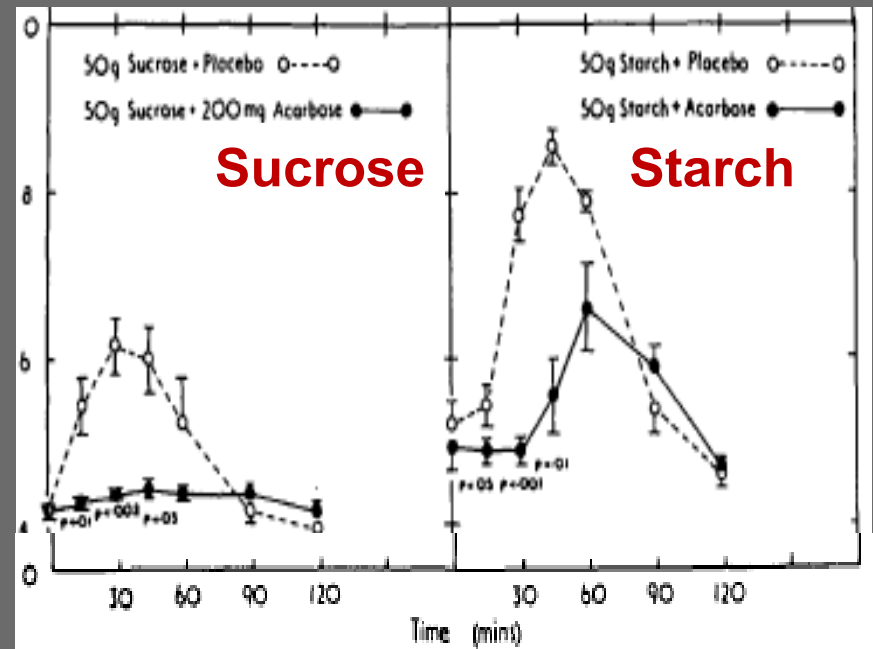
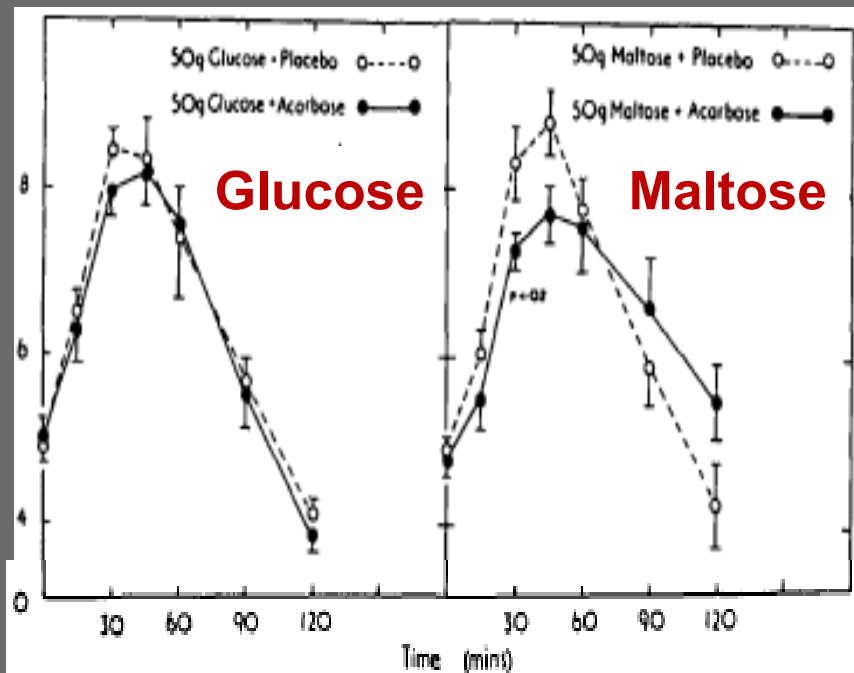
Acarbose (alpha-glucosidase inhibitor)

Insulin secretion is reduced as a result of lower carbohydrate absorption



Acarbose

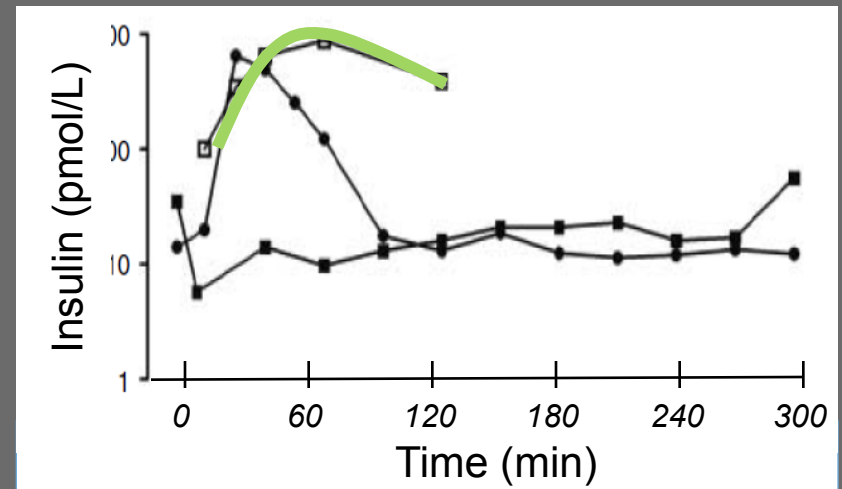
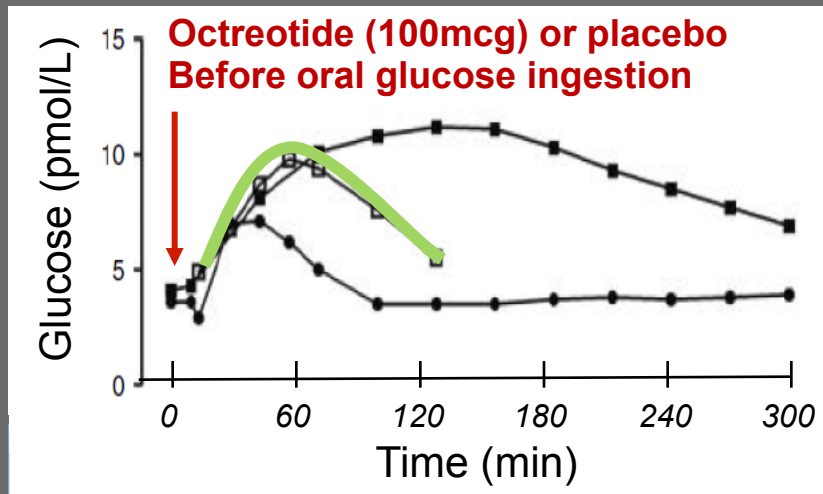
- Differential effect of on carbohydrate absorption
- GI side effects (abdominal gas, bloating, and diarrhea)



Somatostatin Analogues

- Suppress insulin secretion both fasting and post-meal
- Reduce GLP-1 secretion
- Suppress glucagon and growth hormone (counter-regulatory hormones)
- Limited by GI side effects (diarrhea) and cost

Case report: Hypoglycemia after RYGB compared with non-surgical controls (n=8)

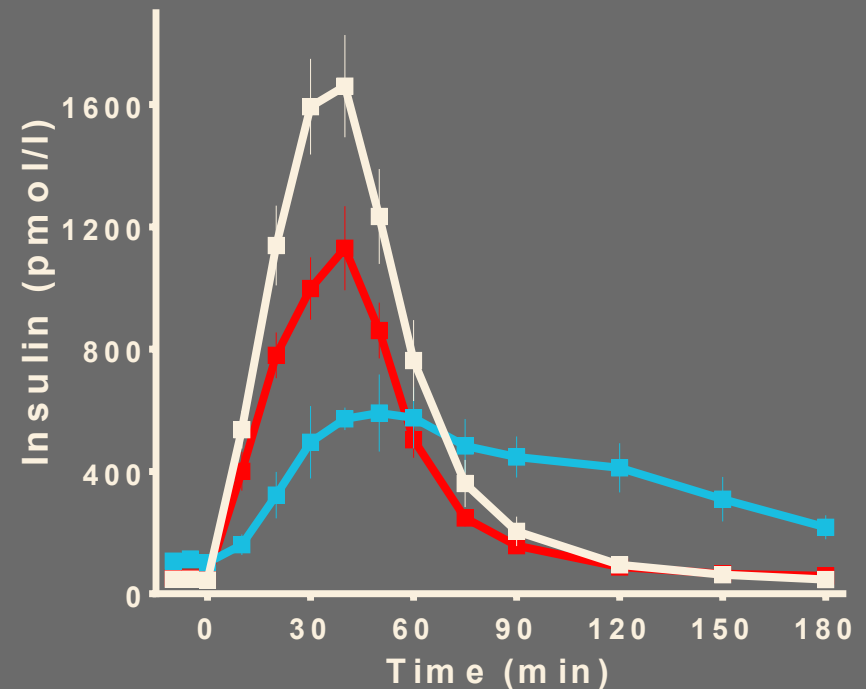
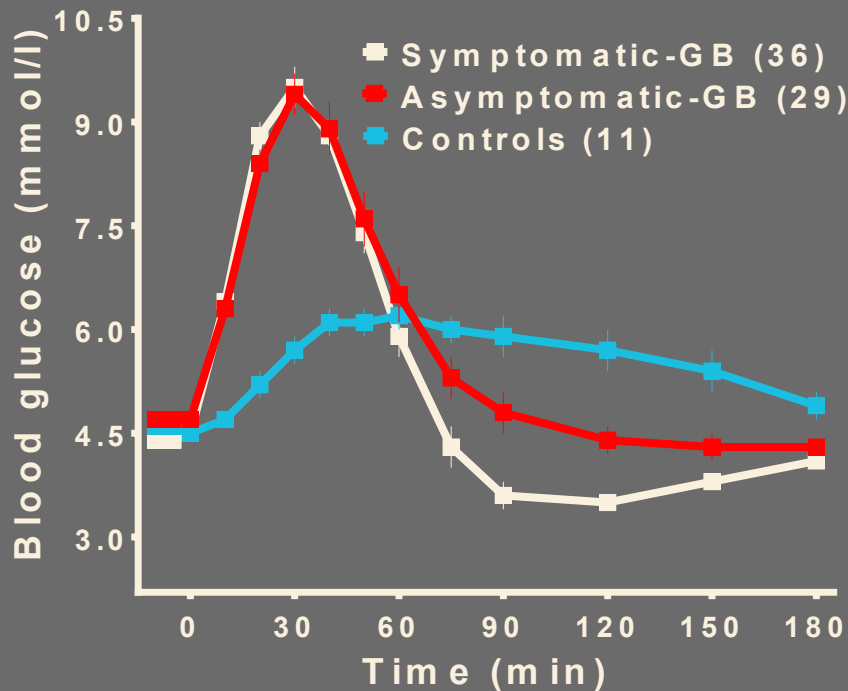


□ Control (OGTT), n=8 ● JM (OGTT) ■ JM (Octreotide + OGTT)

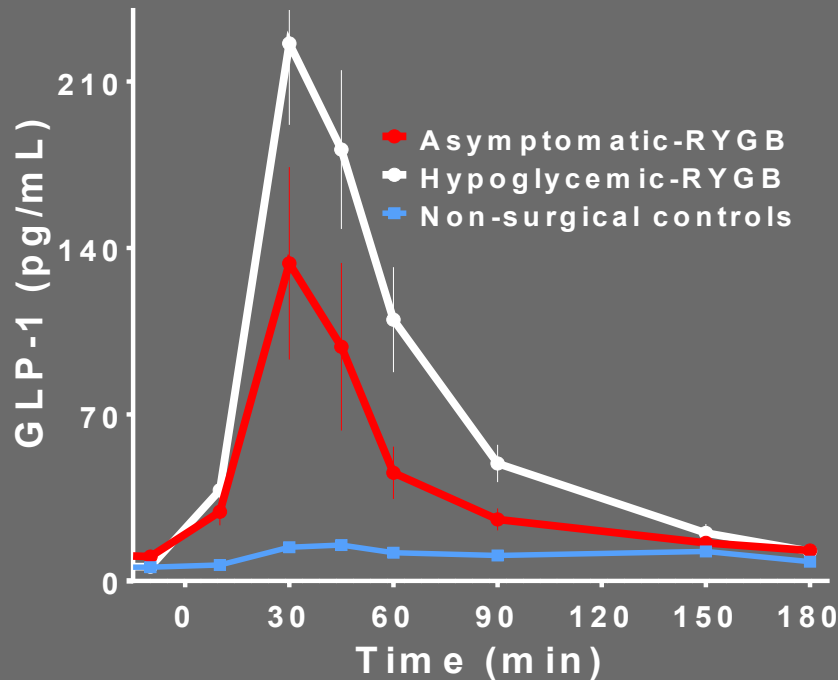
Post-prandial insulin secretion after RYGB is exaggerated in post-RYGB hypoglycemia

Increased incretin effect after GB

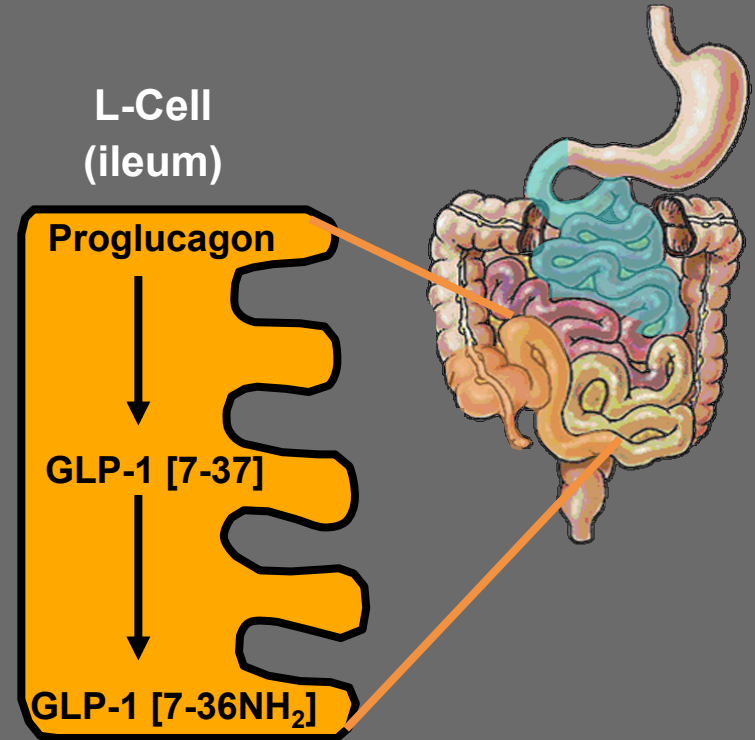
✓ Gut hormones (mainly GLP-1)



GLP-1 levels post-meal are greater after RYGB compared to non-surgical controls



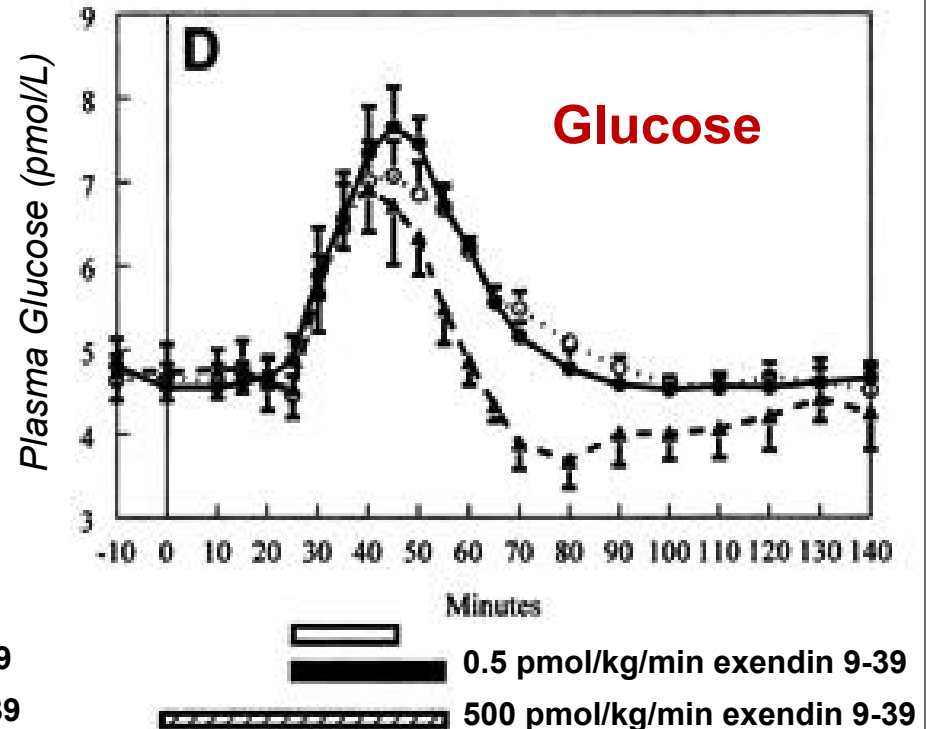
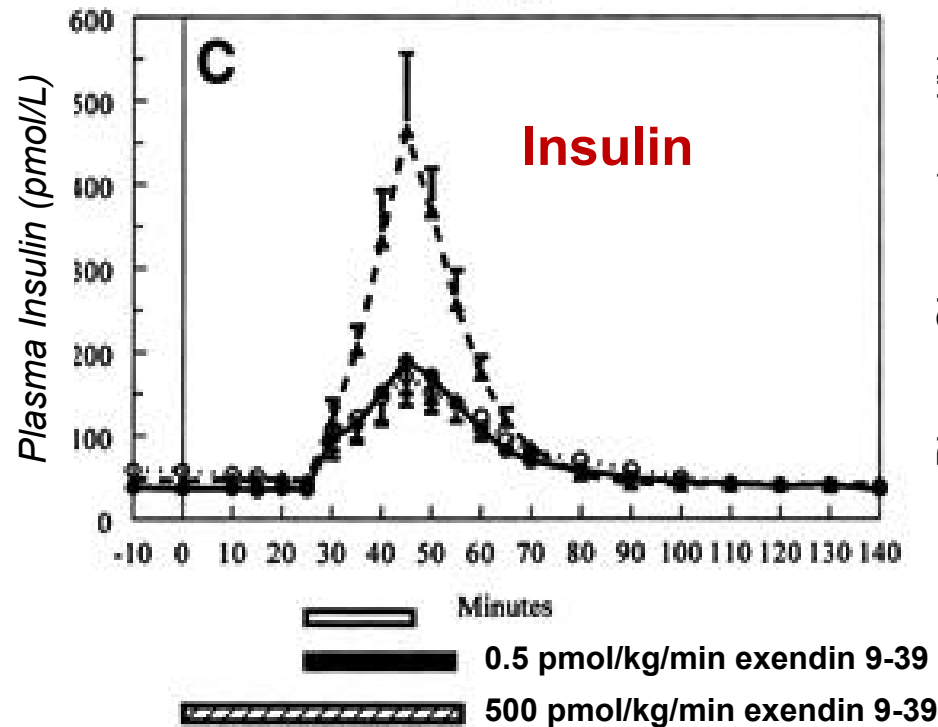
Hypoglycemic patients have larger GLP-1 response compared to those without



**Accentuated GLP-1 action
contributes to enhanced insulin
secretion after GB in general,
and to a greater extent in
patients with hypoglycemia**

Exendin 9-39 is a Potent GLP-1r Antagonist

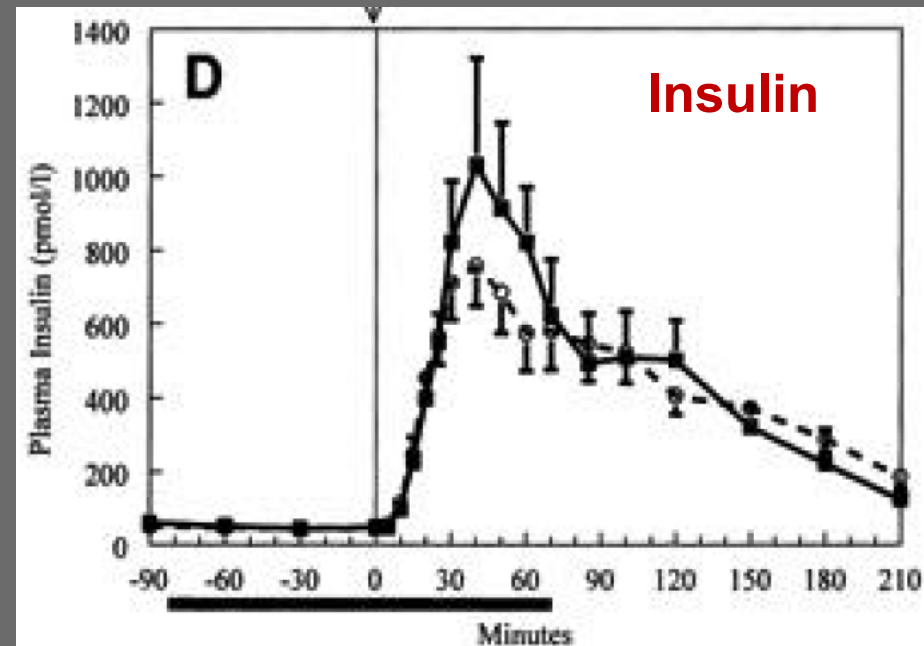
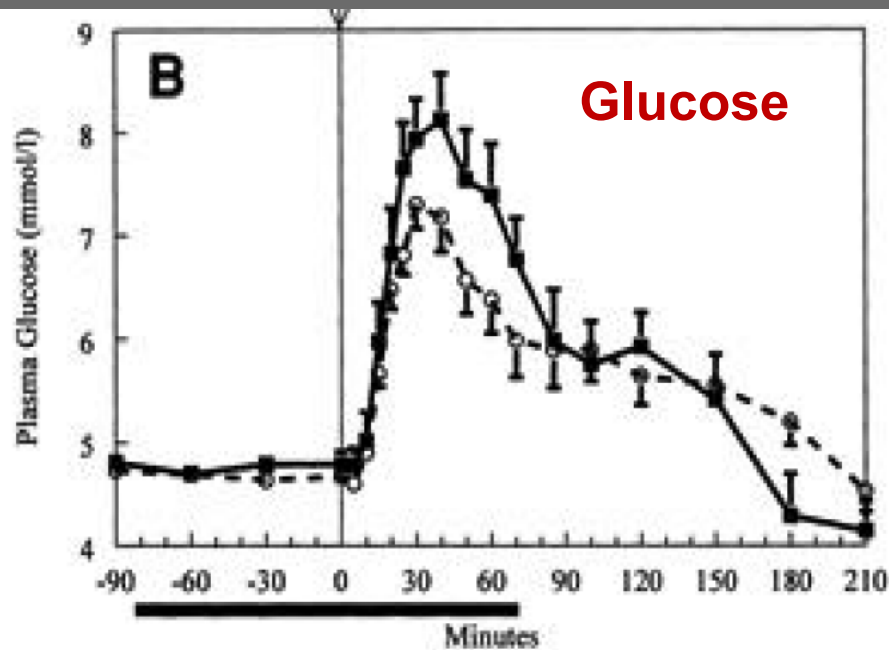
GLP-1-induced insulin response is suppressed by Exendin 9-39
1:1000 dose ratio



Endogenous GLP-1 is important in regulation of glucose tolerance

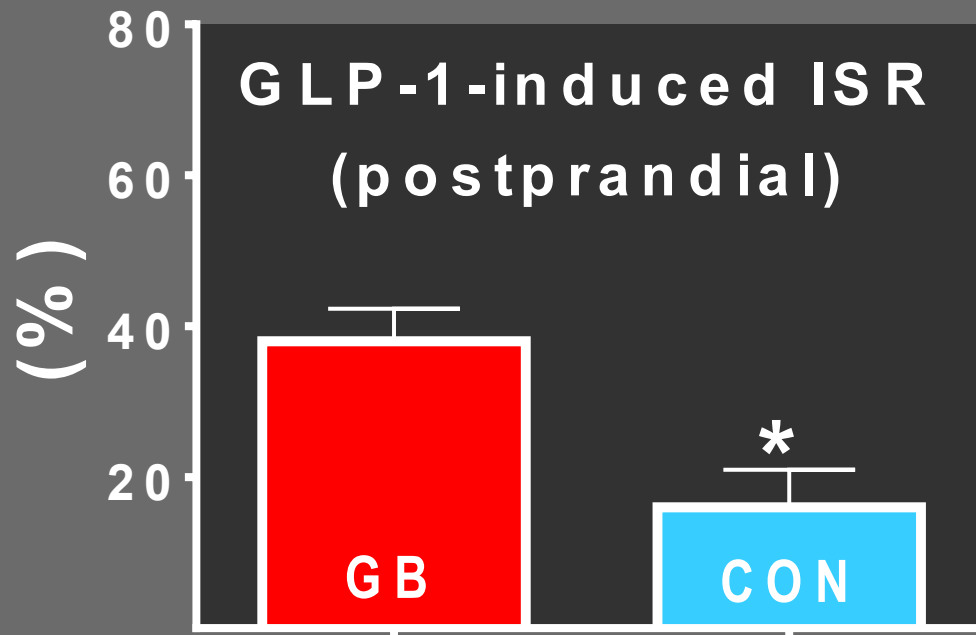
GLP-1-induced insulin secretion is confounded by hyperglycemia

Exendin 9-39: 500 pmol/kg/min IV



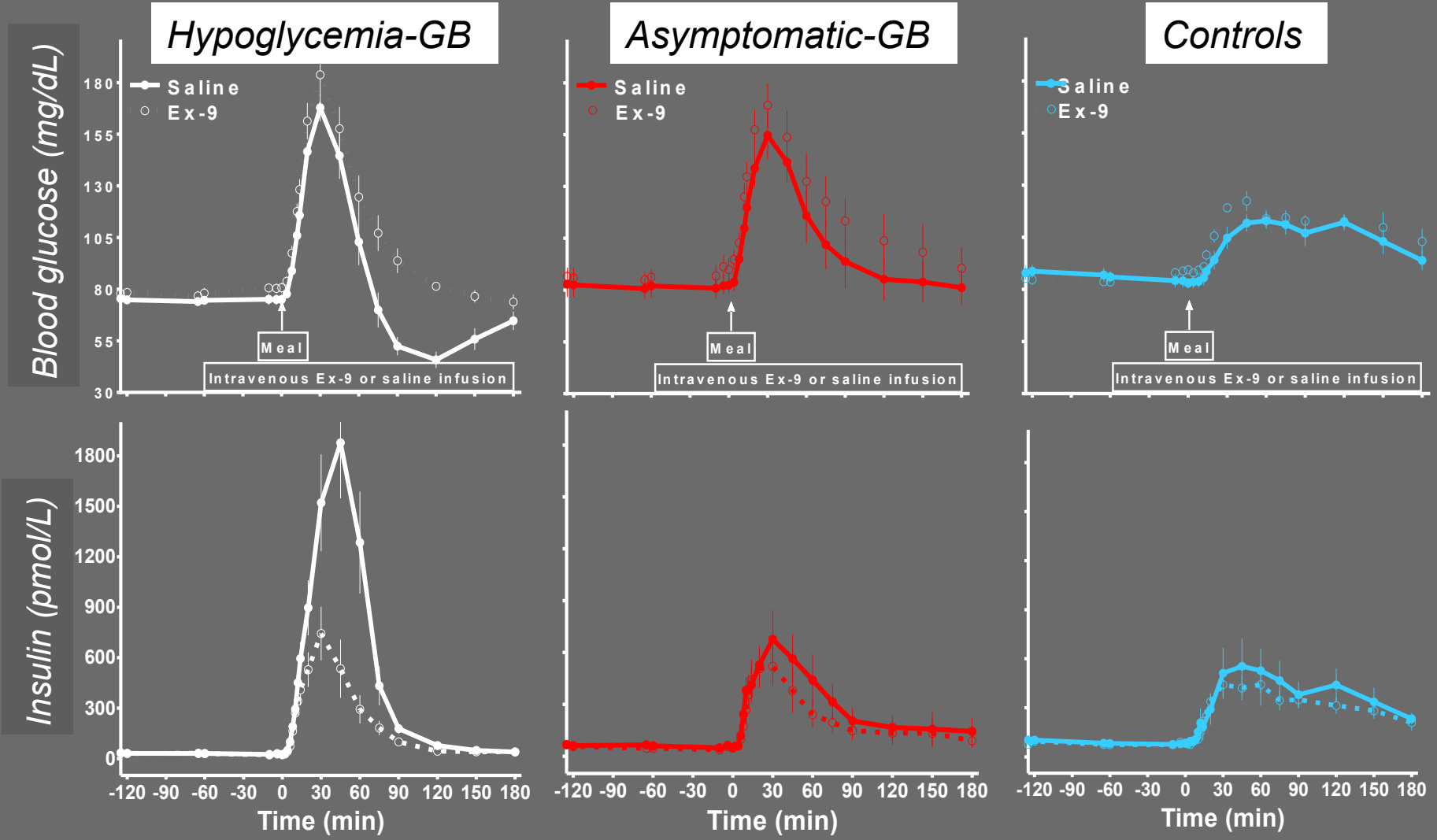
GLP-1-stimulated insulin response to meal ingestion is larger in GB subjects

MTT: Fixed glucose 240-250 mg/dL



Blocking GLP-1r Corrected GB-related Hypoglycemia

Through Reduction of Insulin Secretion



Summary

- Medical nutrition therapy remains the first line of treatment
- No approved pharmacological therapy for RYGB-related hypoglycemia
- Current treatments are suboptimal
- Exendin 9-39 targets underlying pathogenic factor:
 - Increased GLP-1 contribution to insulin secretion
 - ✓ Intravenous infusion of Exendin 9-39 has been shown to correct hypoglycemia in meal studies
 - ✓ Phase 2 studies with Exendin 9-39 in PBH underway (Eiger)

Exendin 9-39 in Post-Bariatric Hypoglycemia

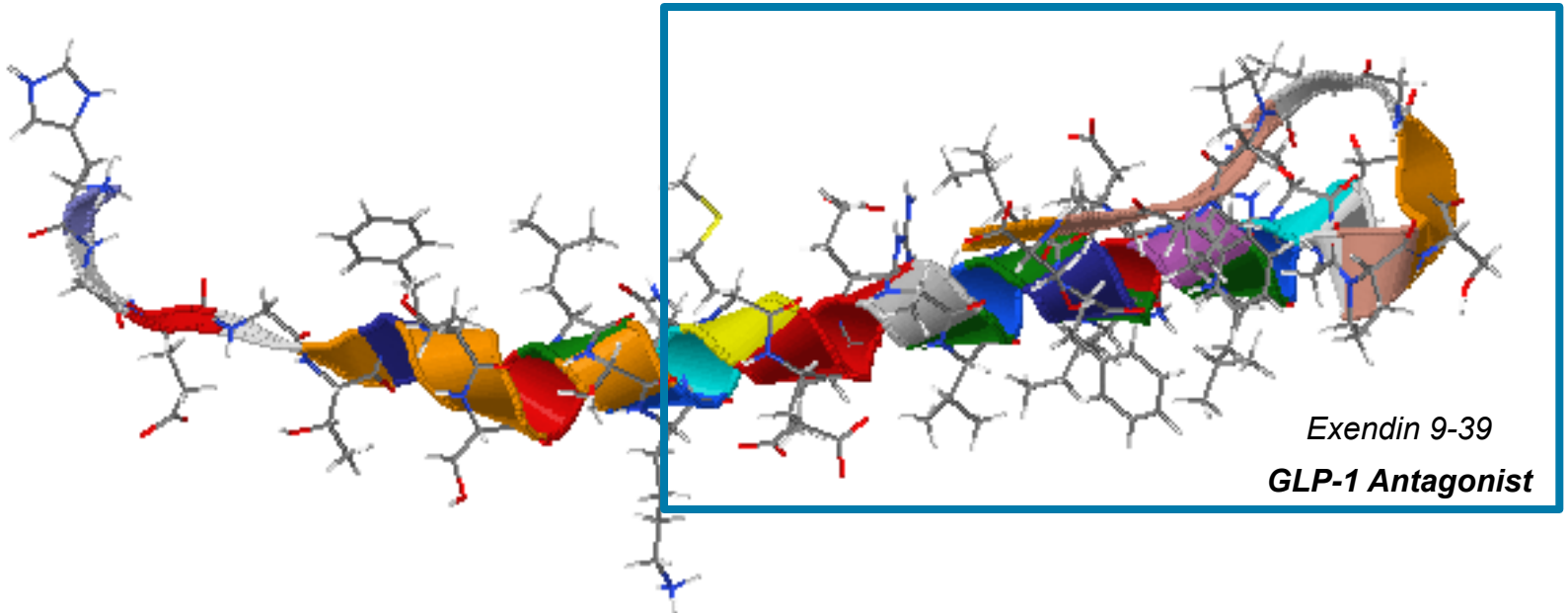
COLLEEN M. CRAIG, M.D.

Division of Endocrinology, Metabolism & Gerontology
Stanford University School of Medicine

Director, Clinical Development
Eiger BioPharmaceuticals

Exendin 9-39

Well-characterized GLP-1 Antagonist



31-amino-acid fragment of exenatide, a GLP-1 agonist



Byetta (exenatide)

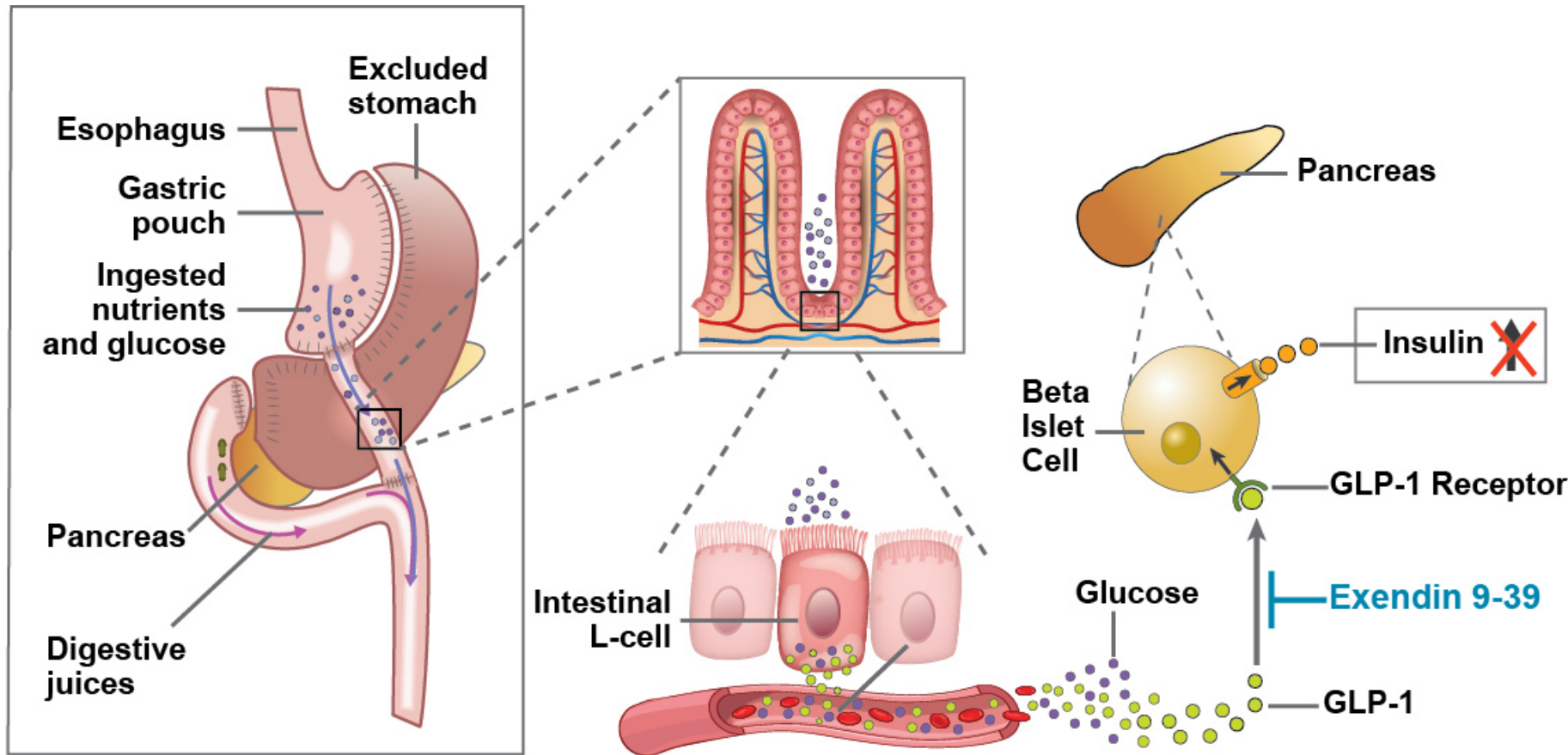
Bydureon (exenatide er)

GLP-1 Agonist



Exendin 9-39 Blocks the GLP-1 Receptor

Prevents Dysregulated Secretion of Insulin



Eiger BioPharmaceuticals

3 Clinical Studies of Exendin 9-39 at Stanford

27 Patients Dosed

Study	# Patients	Duration of dosing	Dose	Status
Phase 1 Continuous IV infusion	8	Single dose	0.03 mg/kg bolus + 0.35 mg/kg	Complete In press: Diabetologia
Phase 2a SAD SC injection	8	Single dose	0.1 – 0.3 mg/kg	Complete Oral presentation 2016 ADA Manuscript in draft
Phase 2a MAD SC injection	11 (completed to date)	Up to 3 days BID dosing	0.05 - 0.4 mg/kg	In progress

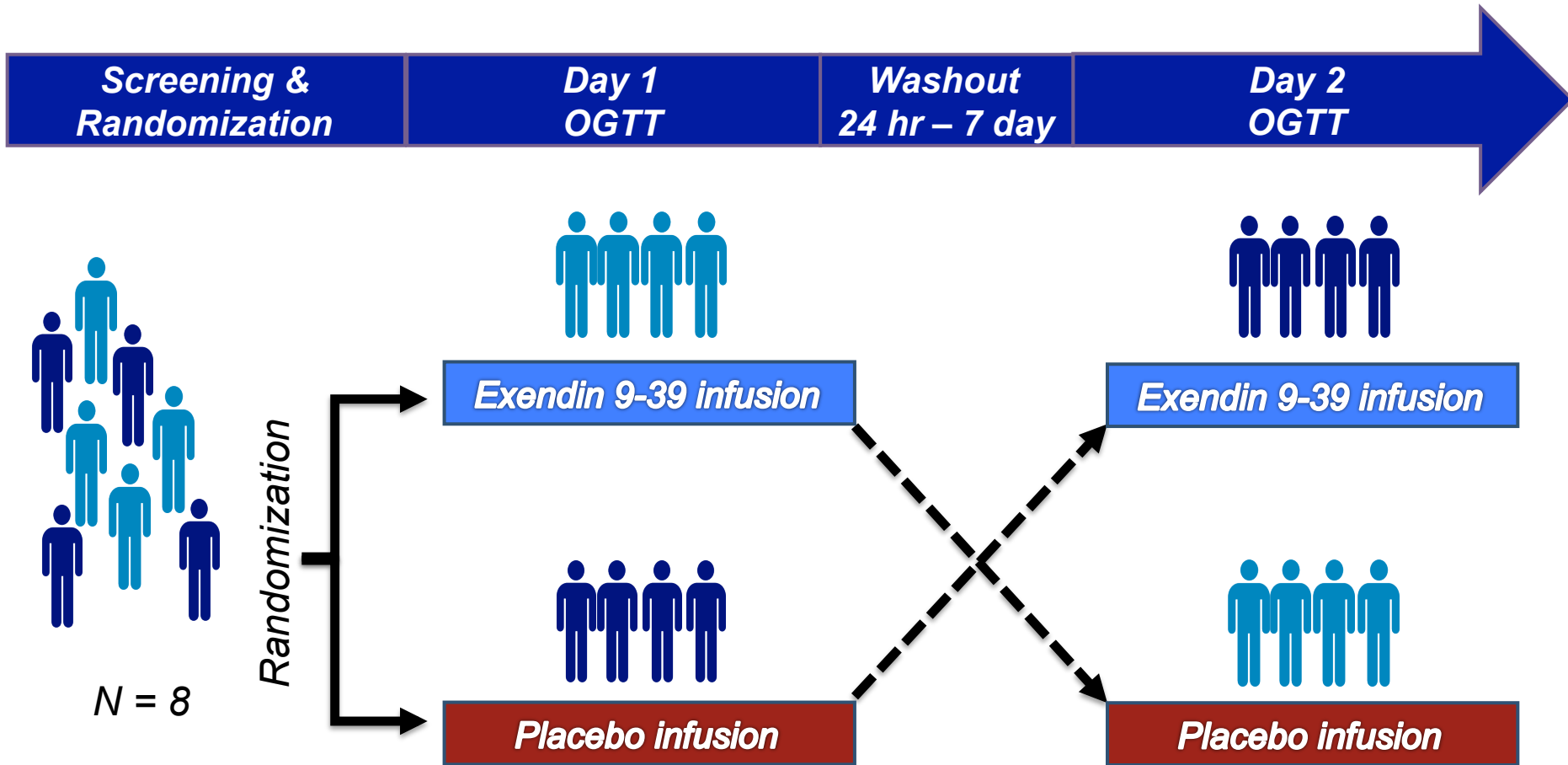
Over 300 patients are reported to have received exendin 9-39 as an investigational agent worldwide.

Exendin 9-39: Phase 1b IV Infusion Study

Crossover Design, Placebo-controlled Trial

Exendin 9-39: Phase 1b IV Infusion Study

Crossover Design, Placebo-controlled Trial



Inclusion Criteria:

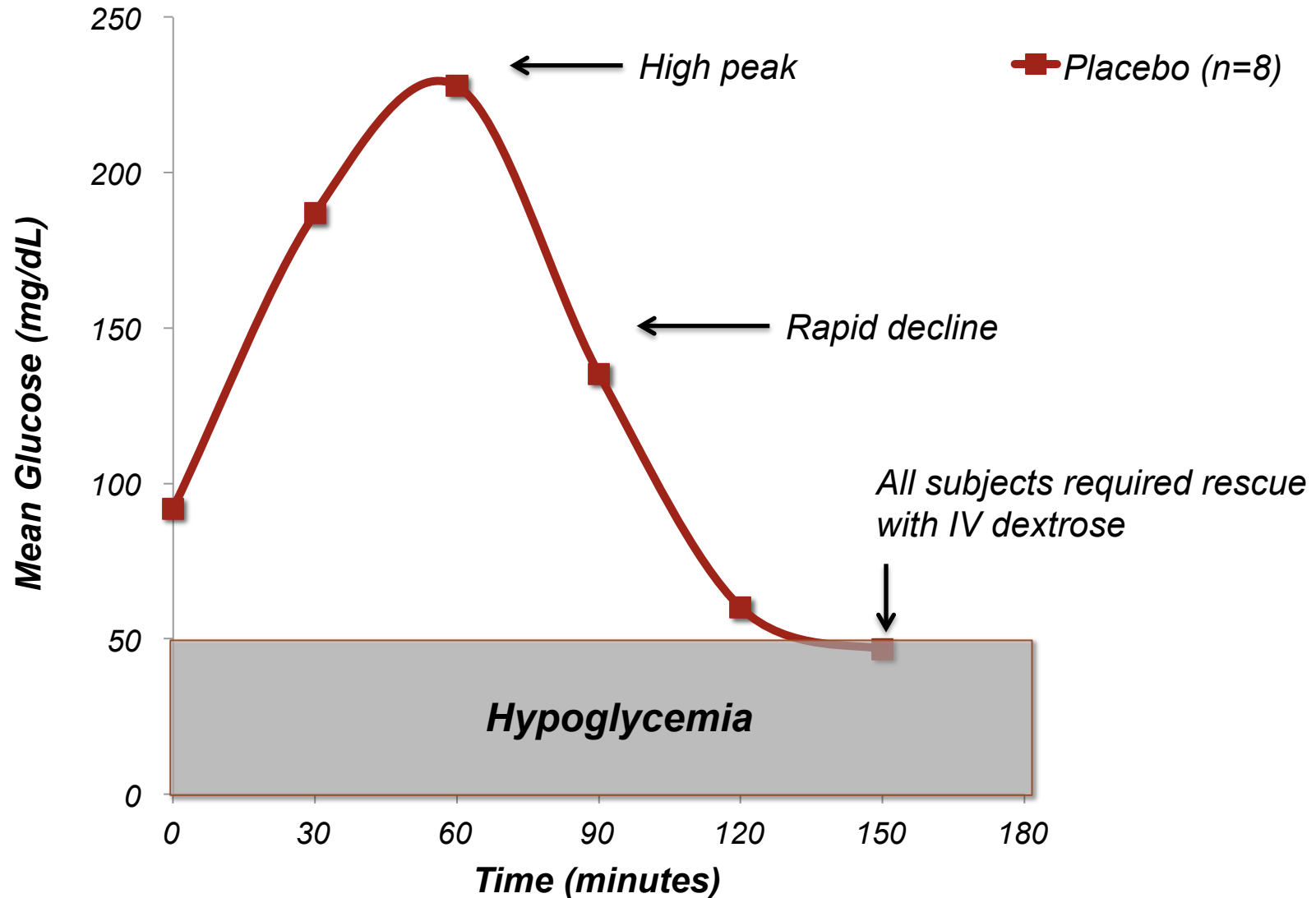
- 1) Whipple's triad
- 2) Hyperinsulinemia (> 3 uU/mL)

Endpoints:

- 1°: Prevention of hypoglycemia (≤ 50 mg/dL)
- 2°: Improvement in symptom score

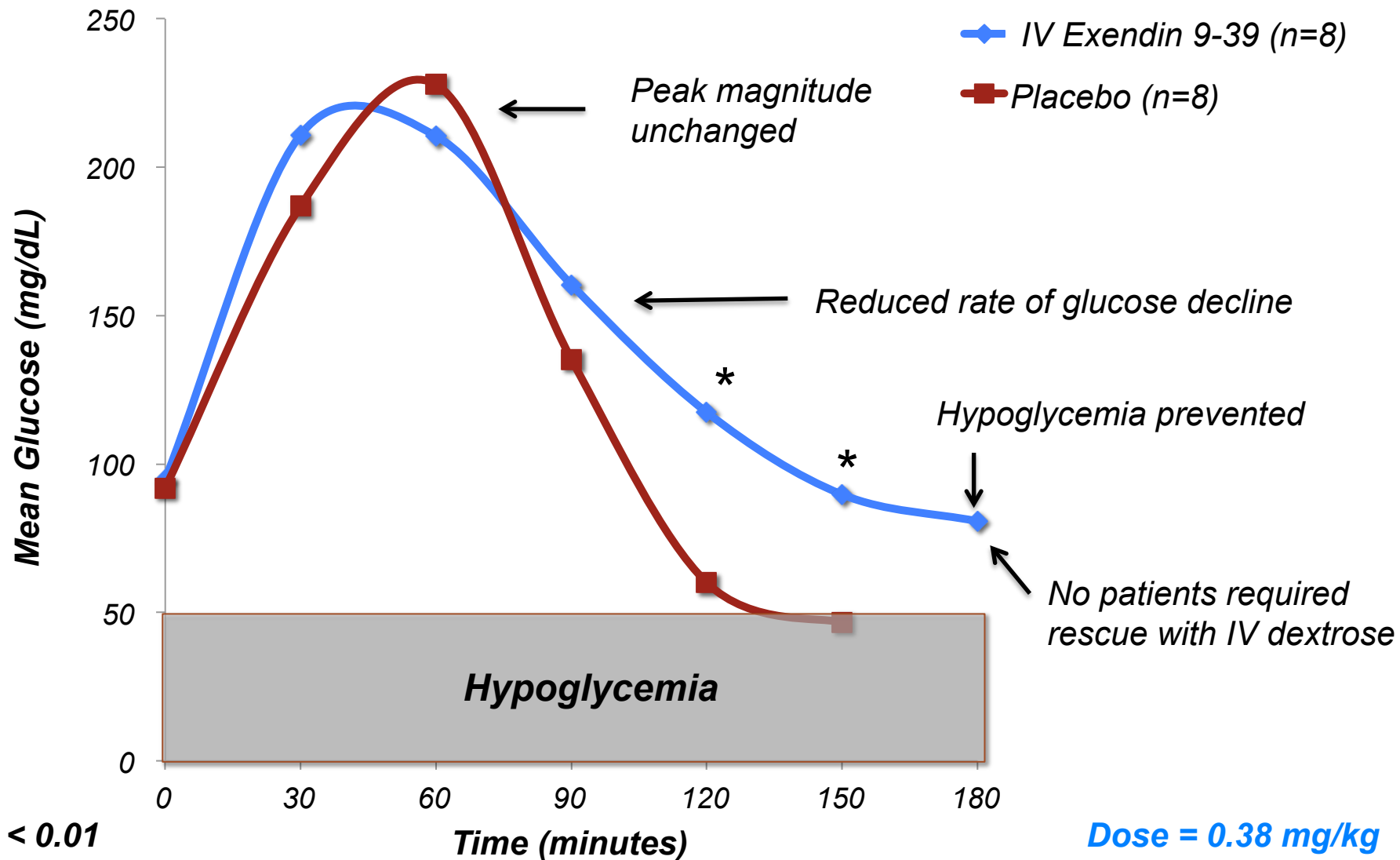
Placebo IV Infusion

All patients became hypoglycemic



Exendin 9-39: 100% Reversal of Hypoglycemia

Phase 1b IV Infusion Study



Improved Symptoms of Hypoglycemia

Exendin 9-39 Phase 1b IV Infusion Study

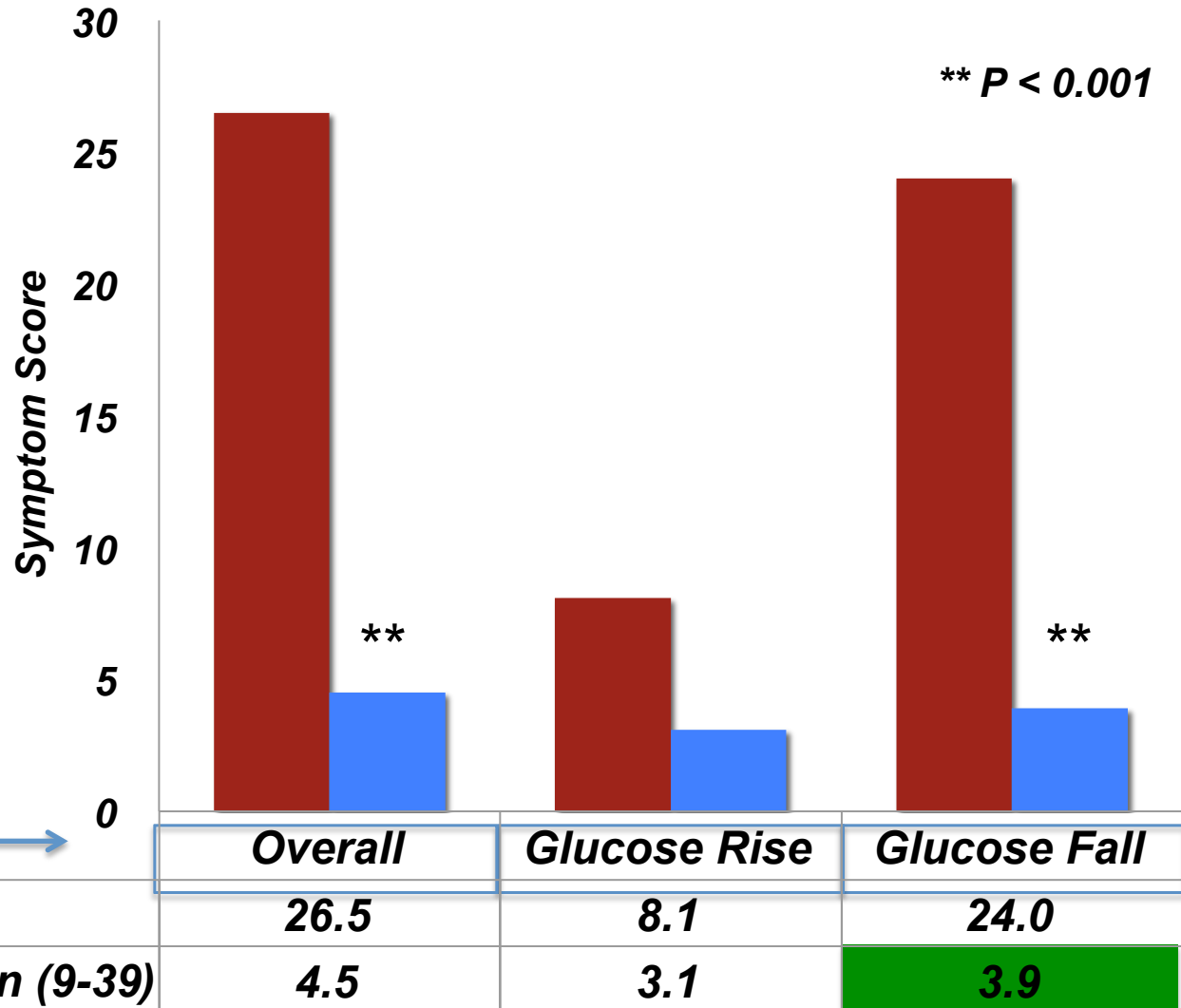
Subjects surveyed every 30 min for presence of:

- Autonomic symptoms
- Neuroglycopenia
- Malaise

Severity ranked 5-point scale:

- 0=none
- 5=severe

Composite Scores



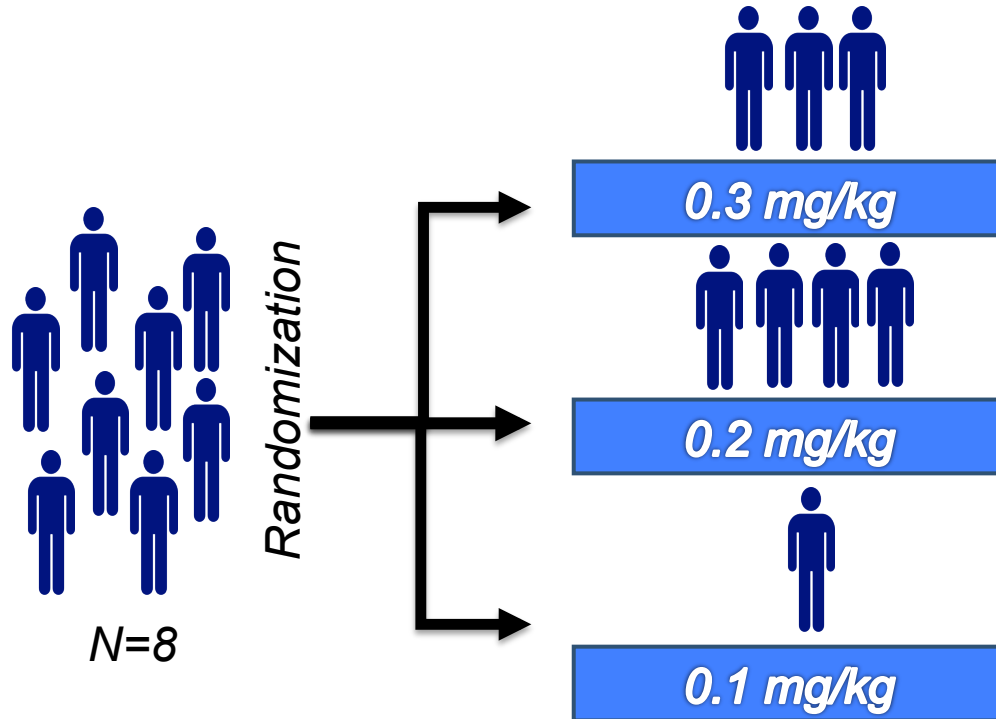
Exendin 9-39: Phase 2a SC SAD Study

Single-Ascending Dose Study

Exendin 9-39: Phase 2a SC SAD Study

Baseline OGTT

SC Exendin 9-39 with OGTT



Endpoints:

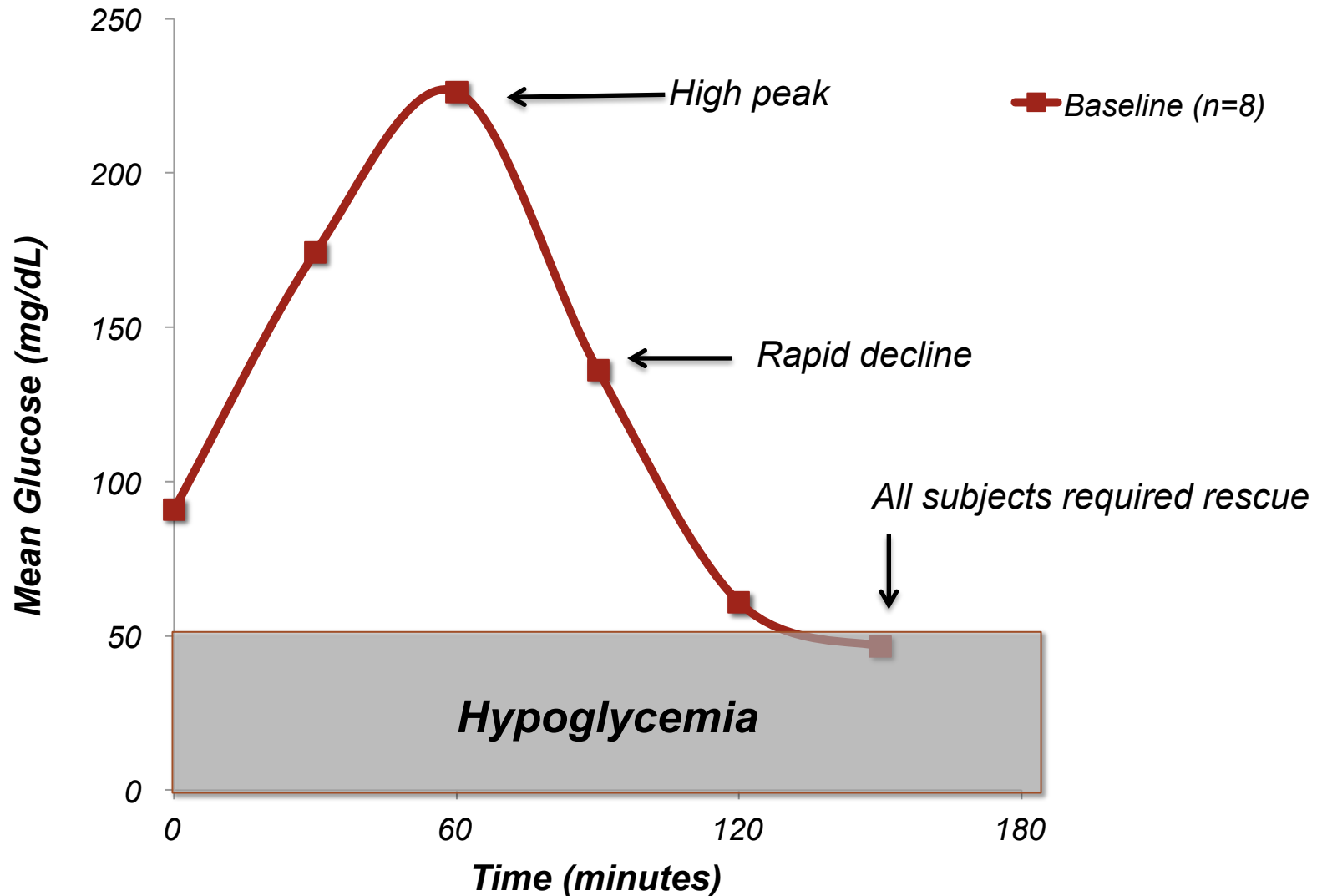
- 1°: Prevention of hypoglycemia (≤ 50 mg / dL)
- 2°: Improvement in hypoglycemia symptom score

Pharmacokinetic profile

Safety & Tolerability

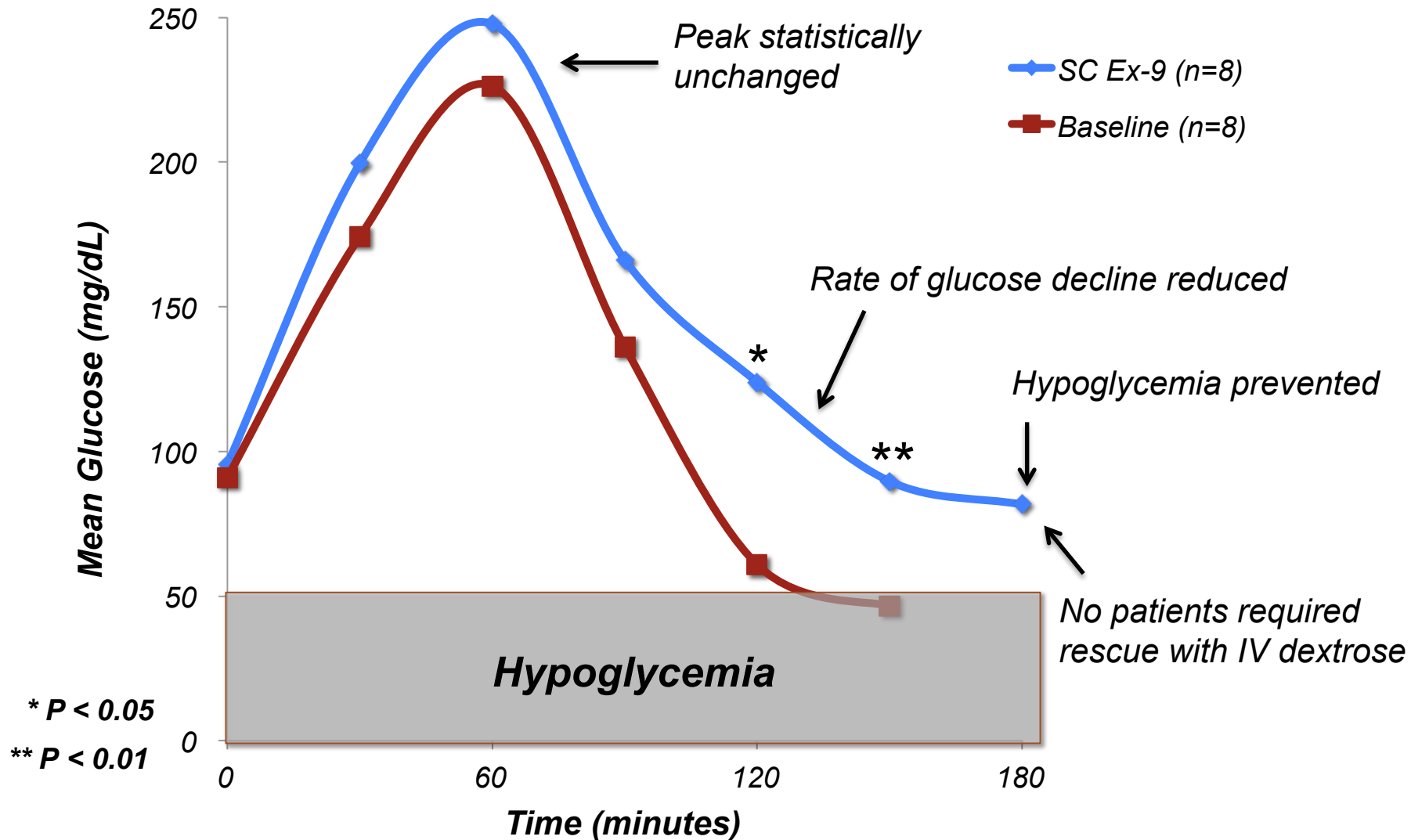
Baseline OGTT: All Patients Became Hypoglycemic

Phase 2a SAD SC Exendin 9-39 Study



Exendin 9-39: All Doses Therapeutic

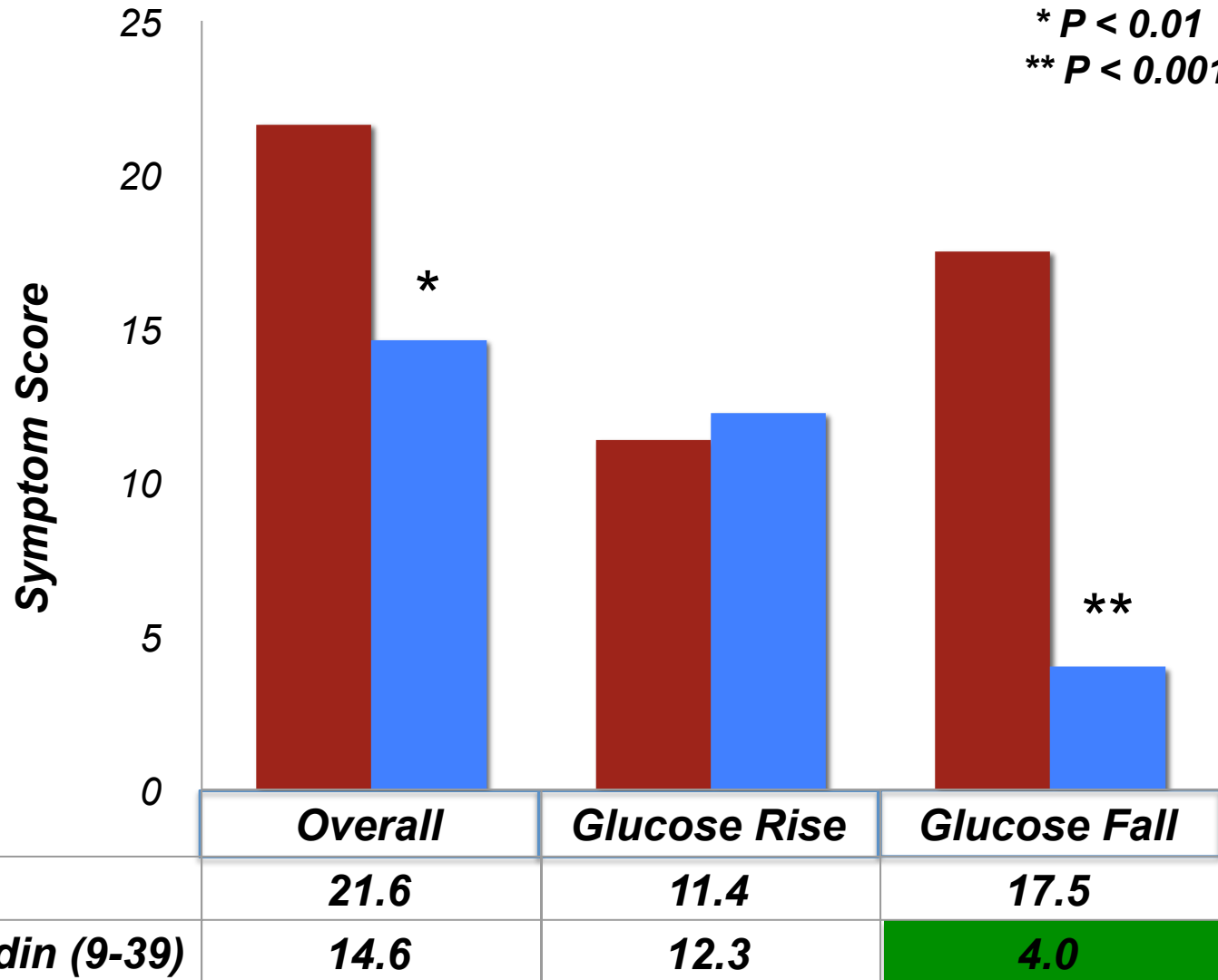
Phase 2a SAD SC Study



Exendin 9-39 Reduced Symptoms of Hypoglycemia

Phase 2a SAD SC Study

* $P < 0.01$
 ** $P < 0.001$



Exendin 9-39: Phase 2a SC MAD Study

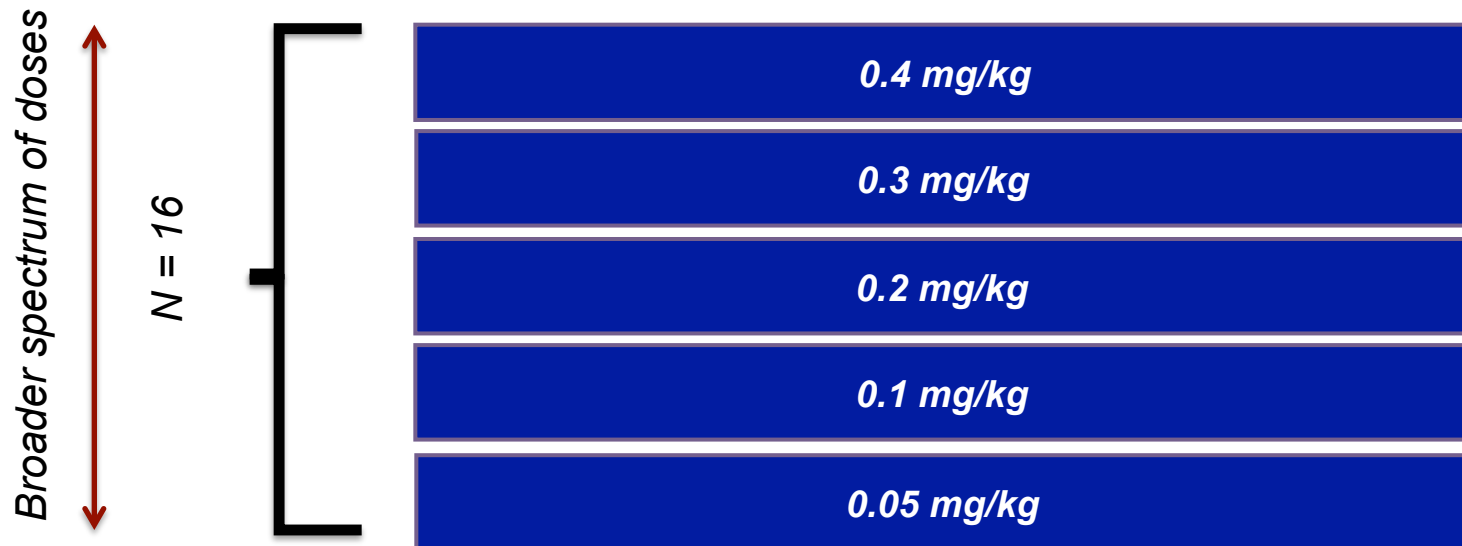
Multiple-Ascending Dose Study

Exendin 9-39: Phase 2 SC MAD Study

Multiple-Ascending Dose Study

Purpose:

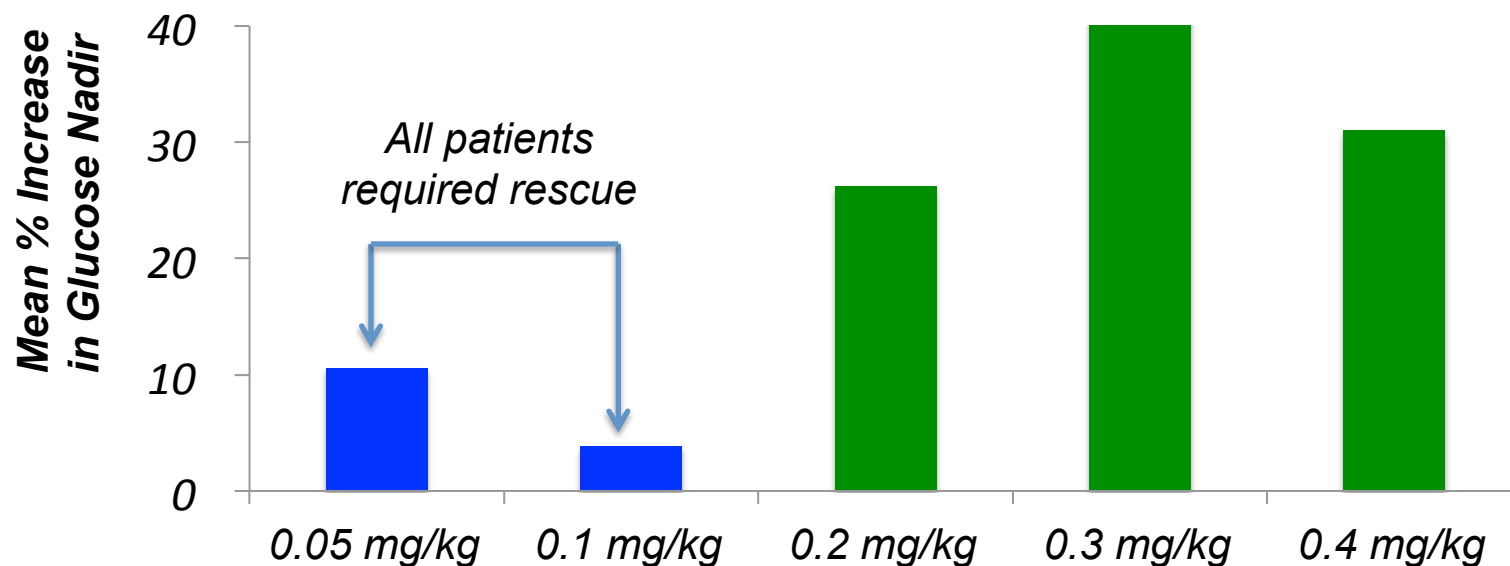
- To evaluate the efficacy, safety, and PK profile of multi-ascending doses of SC exendin 9-39 after up to 3 days of treatment
- To determine the lowest effective dose



Therapeutic Increase in Glucose Nadir

For Patients Dosed ≥ 0.2 mg/kg

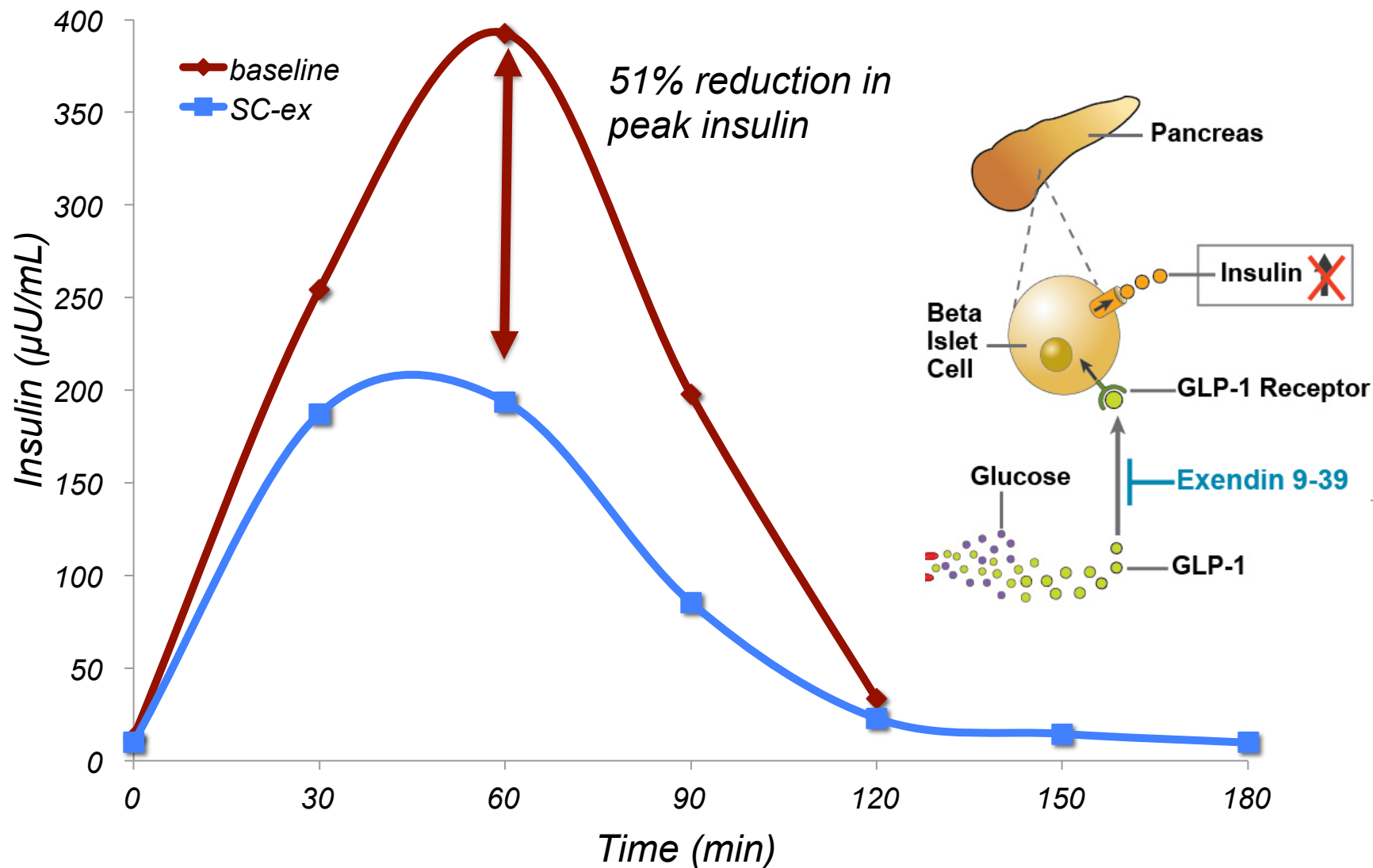
All dose levels reduced magnitude of hypoglycemia



Dose (mg/kg)	0.05	0.1	0.2	0.3	0.4
# Patients	3	3	1	2	2
% Increase Nadir	11 ± 18	4 ± 5	26	41 ± 17	31 ± 3

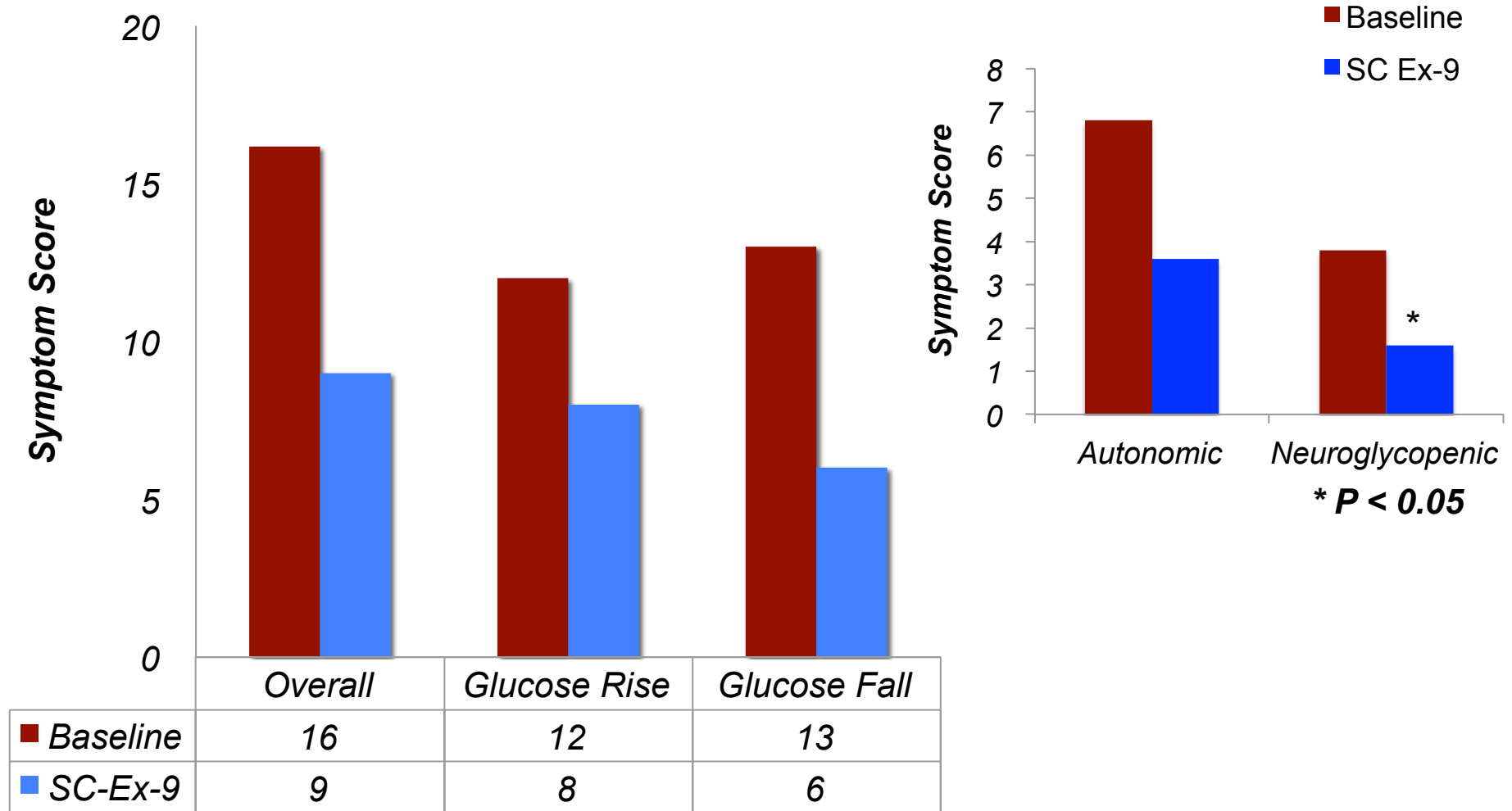
Exendin 9-39 Prevented Severe Hyperinsulinemia

Fasting Insulin, Fasting Glucose Not Raised: a Targeted Therapeutic Approach



Exendin 9-39 Improved Symptoms of Hypoglycemia

For Patients Dosed ≥ 0.2 mg/kg



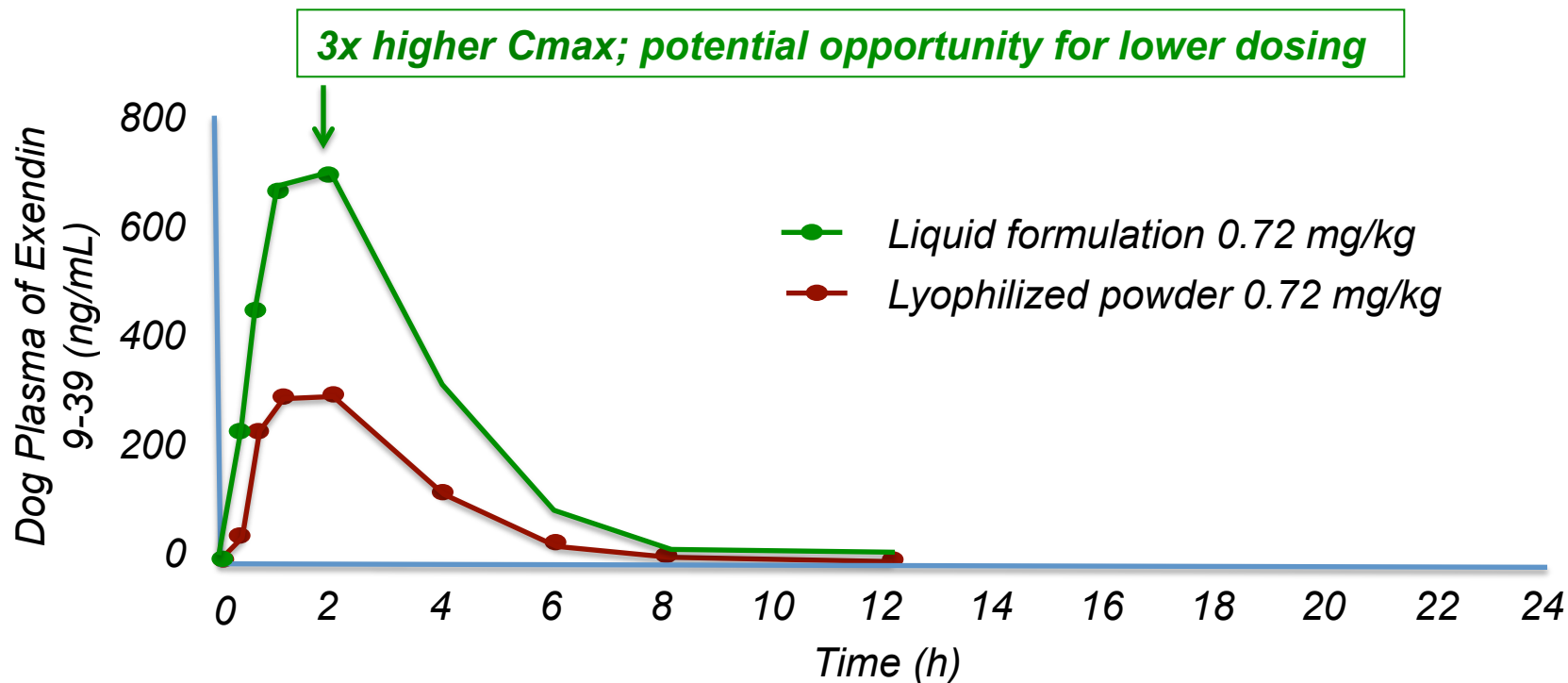
Novel Liquid Formulation: Improved Exposure

Compared to Original Lyophilized Formulation

To be evaluated in planned **Phase 1 PK** study in healthy humans
To be tested in remaining patients in ongoing **MAD** study



Data will inform dosing for planned **Phase 2** study



Phase 2a SC Exendin 9-39 MAD Study

Summary

- *Exendin 9-39 SC administered in doses ranging from 0.05 - 0.4 mg/kg*
- *All doses administered were well-tolerated*
 - *Headache and nausea were reported*
- *All doses reduced the magnitude of post-prandial hypoglycemia*
- *All doses reduced the presence and severity of symptoms of hypoglycemia*
- *Novel liquid formulation appears to increase C_{max} by 3x*
 - *Potential opportunity for lower dosing*

Exendin 9-39

Clinical and Regulatory Path to Registration

2015

2016

2017

IV
Infusion
Study

N=8

IV Manuscript in Press: Diabetologia ✓

SC Injection
SAD
Study

N=8

SC SAD
Oral Preso

ADA
June 2016



Dosing Now

SC Injection
MAD
Study

N=16

Dosing with new liquid
formulation planned

US & EU Orphan Designation ✓

File Eiger IND ✓

Phase 1
PK
Study

Phase 2
Study

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David Gibson

Eiger BioPharmaceuticals

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Dean Felsher

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Stanford SPARK program

Daria Mochly-Rosen

Kevin Grimes

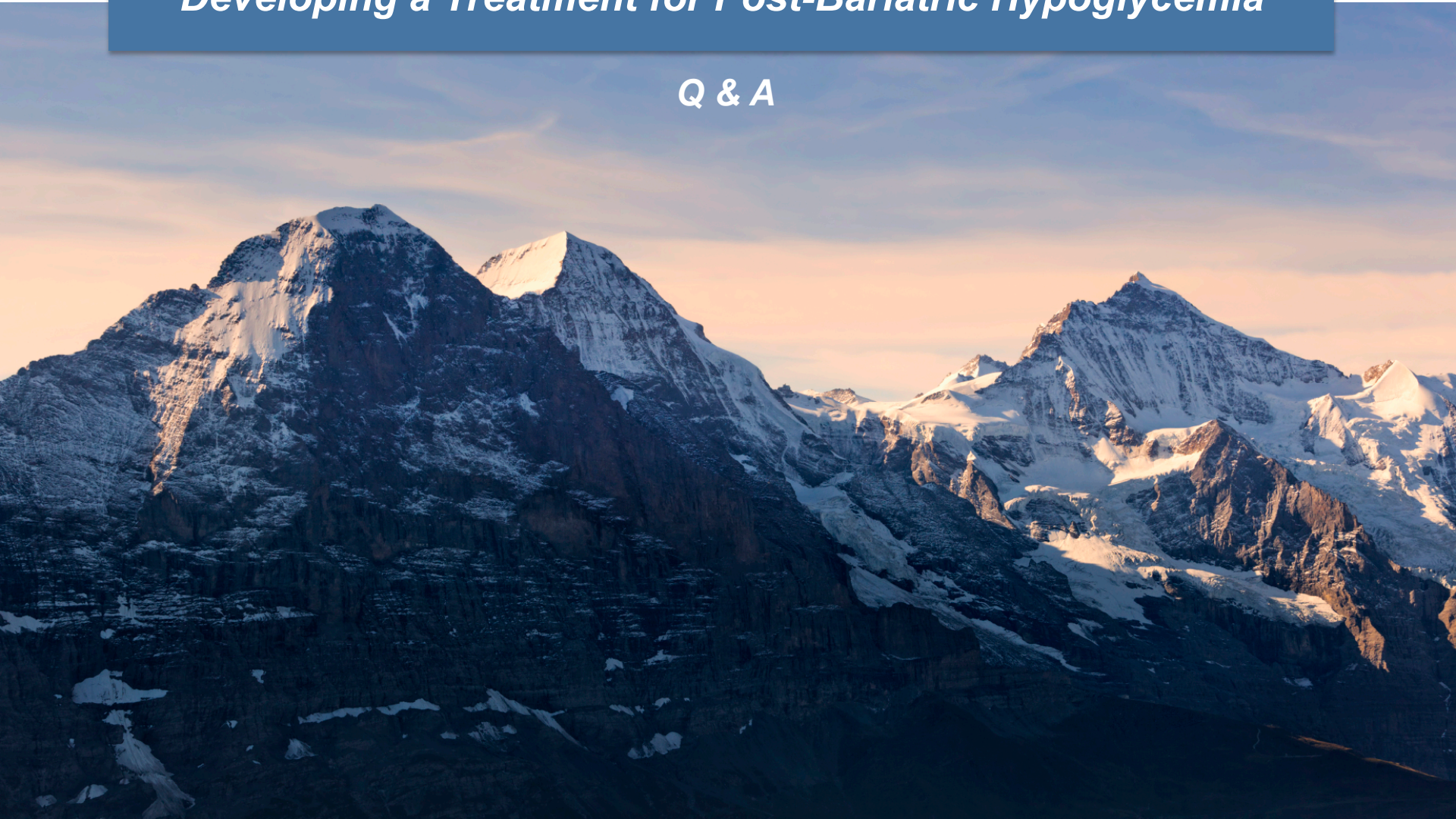
KL2 Mentored Career Development Award

NIH KL2 TR 001083



Developing a Treatment for Post-Bariatric Hypoglycemia

Q & A



Clinical Data and News Flow

Phase 2 Results Across All Programs

	2016	2017
<i>Lonafarnib: LOWR HDV – 2 Interim (EASL 2016)</i>	<input checked="" type="checkbox"/>	
<i>Exendin 9-39: SC SAD Study Data (ADA 2016)</i>	<input checked="" type="checkbox"/>	
<i>Lonafarnib: LOWR HDV EOT Data (AASLD 2016)</i>	<input checked="" type="checkbox"/>	
<i>Exendin 9-39: SC MAD Interim Data</i>	<input checked="" type="checkbox"/>	
<i>Lonafarnib: LOWR HDV EOF Data (EASL 2017)</i>		<input type="checkbox"/>
<i>Exendin 9-39: SC MAD Final Data</i>		<input type="checkbox"/>
<i>Lonafarnib: HDV Agency Meeting</i>		<input type="checkbox"/>
<i>Ubenimex: Lymphedema ULTRA Study</i>		<input type="checkbox"/>
<i>Ubenimex: PAH LIBERTY Study</i>		<input type="checkbox"/>