ISIS PHARMACEUTICALS

Diabetes Program Review

June 16, 2014

Introduction

Stan Crooke, M.D., Ph.D.

CEO and Chairman, Isis Pharmaceuticals

Forward Looking Language Statement

This presentation includes forward-looking statements regarding the discovery, development, activity, therapeutic and commercial potential and safety of ISIS-GCGR$_{Rx,}$ ISIS-PTP1B$_{Rx,}$ and ISIS-GCCR$_{Rx}$ and the discovery, development and therapeutic potential of antisense drugs for the treatment of type 2 diabetes. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2013, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this presentation, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

Participants

Dr. Stan Crooke

CEO and Chairman
Isis Pharmaceuticals

Dr. Robert Henry

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U.C. San Diego
Chief, Section of Diabetes, Endocrinology & Metabolism
Director, Center for Metabolic Research
VA San Diego Healthcare System

Dr. Sanjay Bhanot

VP Clinical Development & Translational Medicine
Isis Pharmaceuticals

Dr. Brett Monia

SVP Antisense Drug Discovery
Isis Pharmaceuticals

B. Lynne Parshall

Chief Operating Officer
Isis Pharmaceuticals

Agenda

- **Introduction**
  - *Dr. Stan Crooke, CEO & Chairman, Isis Pharmaceuticals*
- **Treating Patients with Type 2 Diabetes: Unmet Needs**
  - *Dr. Robert Henry, Professor of Medicine, University of California San Diego*
    Chief, Section of Diabetes, Endocrinology & Metabolism
    Director, Center for Metabolic Research
    VA San Diego Healthcare System
- **ISIS-GCGR$_{Rx}$ Preclinical and Clinical Data and Plans**
  - *Dr. Sanjay Bhanot, VP Clinical Development & Translational Medicine, Isis Pharmaceuticals*
- **ISIS-PTP1B$_{Rx}$ and ISIS-GCCR$_{Rx}$**
  - *Dr. Brett Monia, SVP Drug Discovery & Corporate Development, Isis Pharmaceuticals*
- **ISIS-GCGR$_{Rx}$ Partnering Plan and Upcoming Pipeline Milestones**
  - *Lynne Parshall, COO, Isis Pharmaceuticals*
- **Q & A**

ISIS-GCGR$_{Rx}$: Clinical Profile Observed To Date

Potential to Be Best in Class for Patients with Severe Diabetes

- Robust and long-lasting effects on glucose control observed
- Potential for potent inhibition of hepatic glucagon action with the added benefit of GLP-1 increases
- Potential to have greater glucose reduction than small molecules by directly reducing production of the receptor
- In clinical trials to date, no clinically meaningful effects observed on LDL, blood pressure and body weight, and no nausea or vomiting
- Significant dose-dependent reductions in HbA1c support identification of optimal dose and schedule to achieve glucose control with minimal glucagon receptor-related liver enzyme elevations

ISIS-GCGR$_{Rx}$ Treatment Produced Robust Improvements in Glycemic Parameters and Was Well Tolerated

Phase 2 Study Data

- **Robust, highly statistically significant improvements in glycemic parameters, including HbA1c, after only 13 weeks of treatment**
- **HbA1c of ≤ 7% achieved by a large fraction of patients in both dose groups**
- **Potent inhibitor of hepatic glucagon action with potential to preserve pancreatic function and enhance insulin secretion**
  - Serum GLP-1 increases observed
  - Improvements during OGTT demonstrate GLP-1 effect

Isis' Type 2 Diabetes Pipeline

Three Phase 2 Study Readouts in 2014/2015

DRUG	INDICATION	CURRENT STATUS	NEXT STEP
ISIS-GCGR$_{Rx}$	Diabetes	Phase 2 study ongoing	Phase 2 data 2014
ISIS-PTP1B$_{Rx}$	Diabetes	Phase 2 study ongoing	Phase 2 data YE2014
ISIS-GCCR$_{Rx}$	Diabetes	Phase 2 study ongoing	Phase 2 data 2014/2015

- Isis has created a franchise of novel drugs to treat type 2 diabetes
- Isis' metabolic drugs specifically reduce molecular targets, many of which are undruggable or have been difficult to target with small molecules
- Each drug in the franchise focuses on a unique therapeutic opportunity and is complementary

Isis' Drugs for Type 2 Diabetes

Focus on Distinct High-Value Opportunities

ISIS-GCGR$_{Rx}$	Patients with severe diabetes failing OAD or injectable therapies
ISIS-GCCR$_{Rx}$	Patients with Cushing's Disease or with diabetes driven by glucocorticoid dysregulation failing OAD or injectable therapies
ISIS-PTP1B$_{Rx}$	Patients with diabetes and insulin resistance that could benefit from an insulin sensitizer

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Treating Patients with Type 2 Diabetes: Unmet Needs

Robert Henry, M.D.
Professor of Medicine
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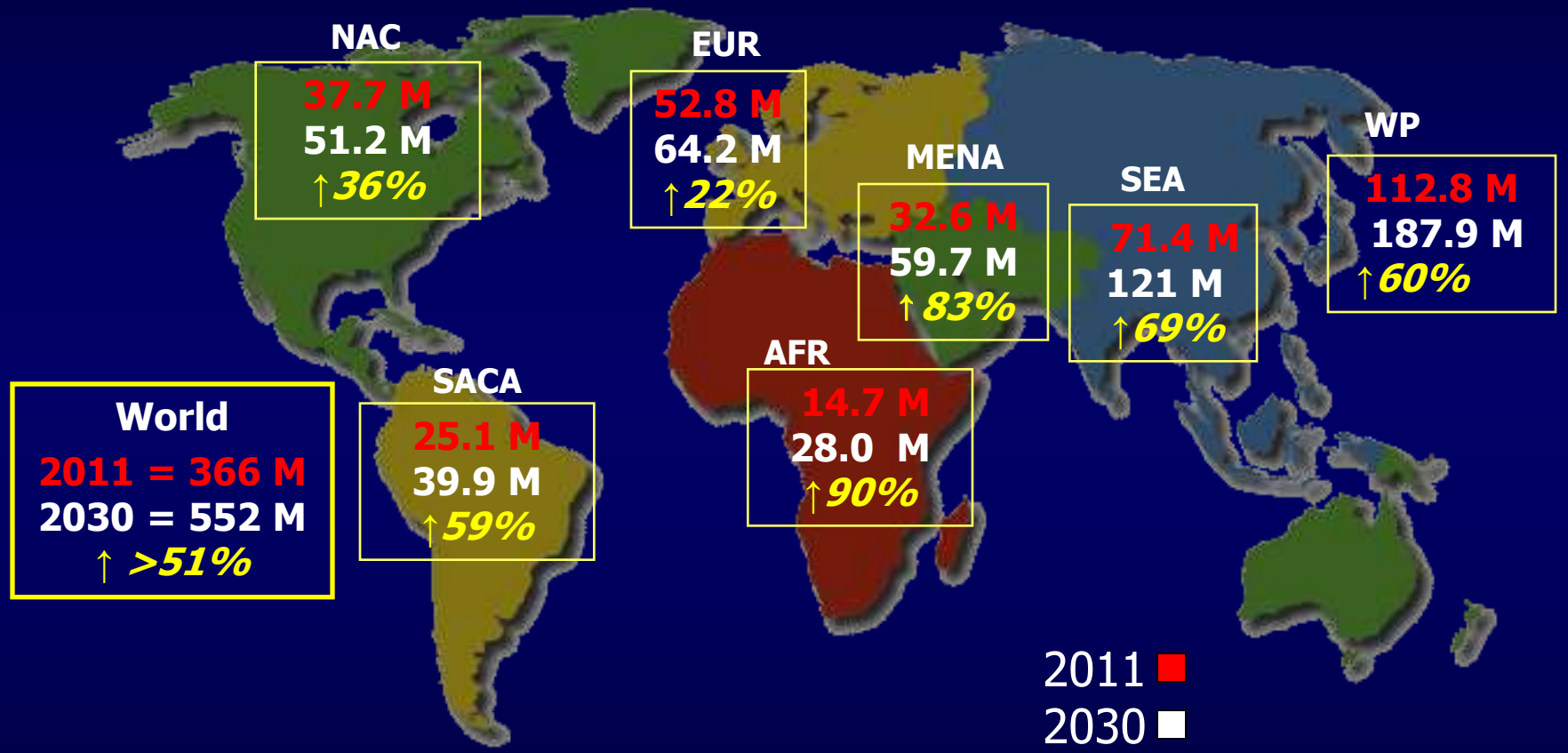
Chief, Section of Diabetes, Endocrinology & Metabolism
Director, Center for Metabolic Research
VA San Diego Healthcare System

Global Projections for the Diabetes Epidemic: 2011-2030



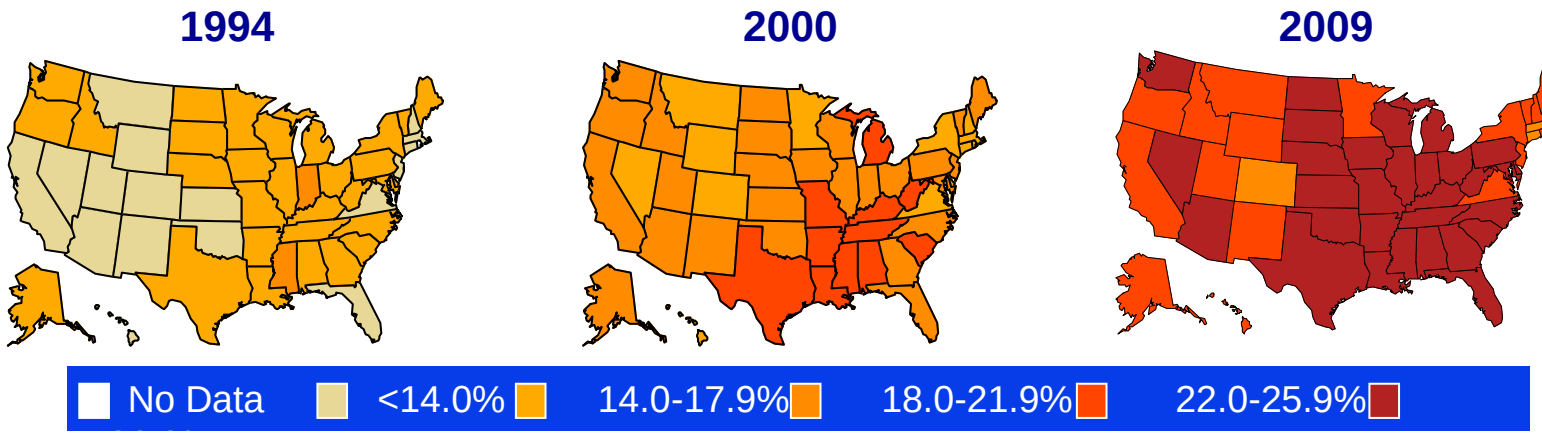
M = million, AFR = Africa, NAC = North America and Caribbean, EUR = Europe, SACA = South and Central America, MENA = Middle East and North Africa, SEA = South-East Asia, WP = Western Pacific

Diabetes Atlas Committee. *Diabetes Atlas 5th Edition:* IDF 2011.

Age-adjusted Percentage of U.S. Adults with Obesity or Diagnosed Diabetes

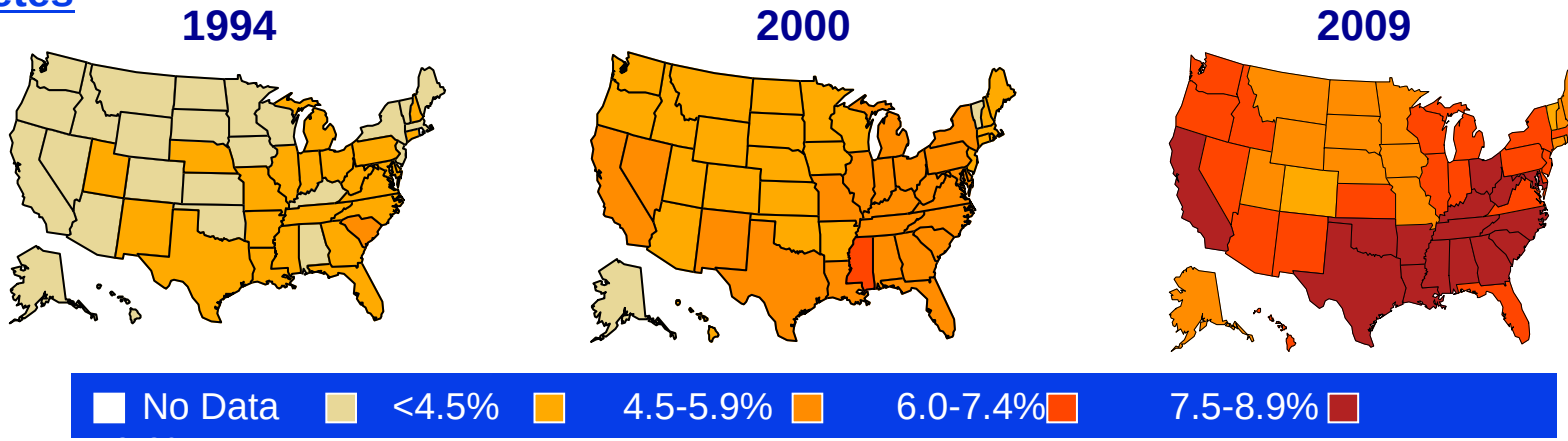
Obesity (BMI ≥30 kg/m^2)

OBESITY



Diabetes

DIABETES



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

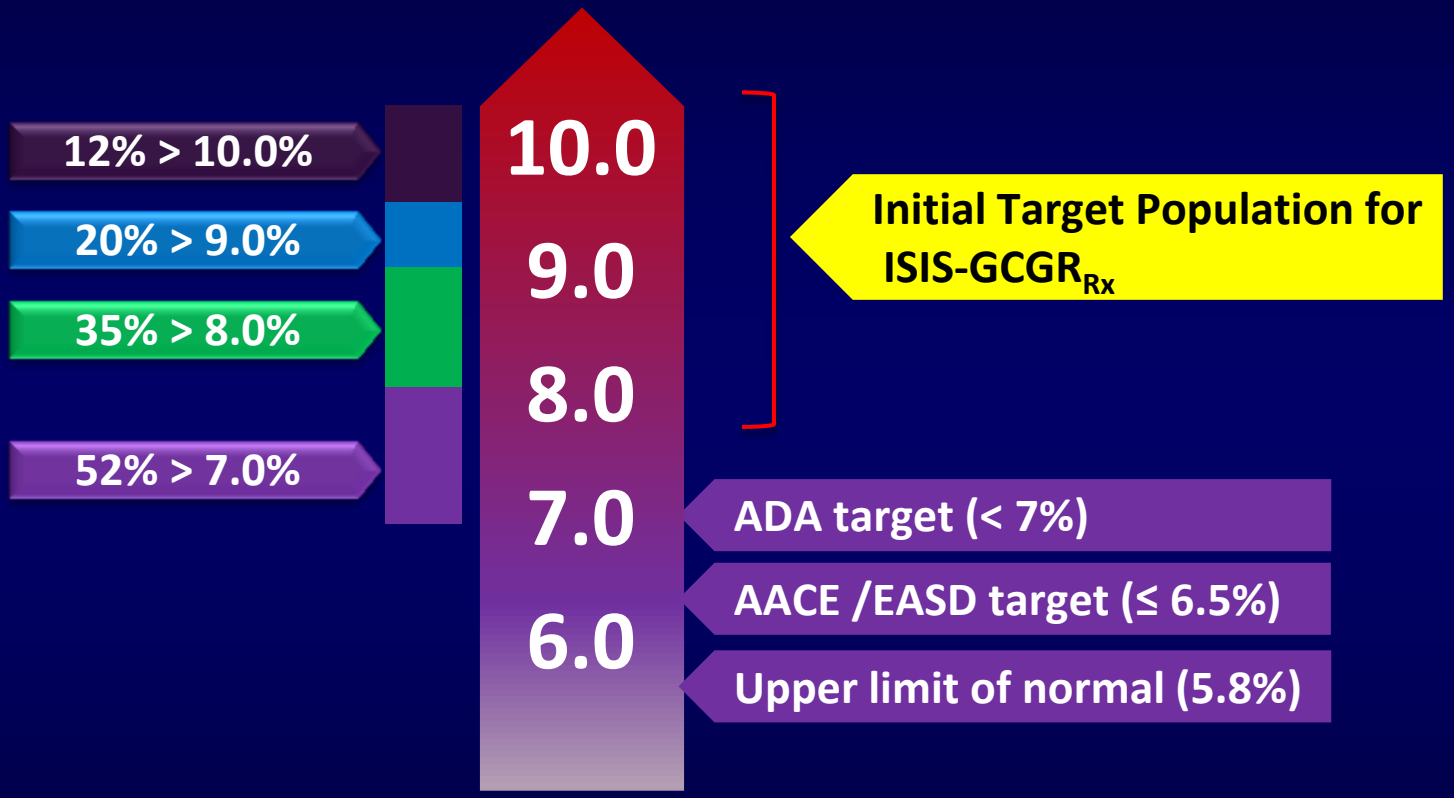
Lowering A1C Reduces Complications in Type 1 and Type 2 Diabetes

A1C	DCCT 9.1% → 7.3%	Kumamoto 9.4% → 7.1%	UKPDS 7.9% → 7.0%
Retinopathy	↓ 63%	↓ 69%	↓ 17%–21%
Nephropathy	↓ 54%	↓ 70%	↓ 24%–33%
Neuropathy	↓ 60%	Significantly improved	—
Macrovascular disease	↓ 41%*	—	↓ 16%*

***Not statistically significant**

DCCT Research Group. *N Engl J Med*. 1993;329:977-986. Ohkubo Y, et al. *Diabetes Res Clin Pract*. 1995;28:103-117. UKPDS Group. *Lancet*. 1998;352:837-853.

Diabetes Report Card: HbA_{1C} Goals Unmet in Most T2DM Patients: Big Need for Potent Glucose-Lowering Drugs



1. ADA. *Diabetes Care* 34(suppl 1):S11-S61, 2011.
2. ACE. *Endocr Prac* 15:540-59, 2009.
3. Saydah, et al. *JAMA* 291:335, 2004.
4. Koro, et al. *Diabetes Care* 27:17, 2007.
5. Cheung et al, *AJM* 122:443, 2009.
6. Resnick et al, *Diabetes Care* 29:531, 2006
7. AACE, *State of Diabetes in America*, 2006
8. Hoerger et al, *Diabetes Care* 31:81, 2008.
9. Grant et al, *Diabetes Care* 30:807, 2005.
10. NCQA, www.ncqa.com
11. Casagrande, *Diabetes Care* 36:2271-9, 2013
12. Esposito, *Diab Ob Metab* 14:228-33, 2012

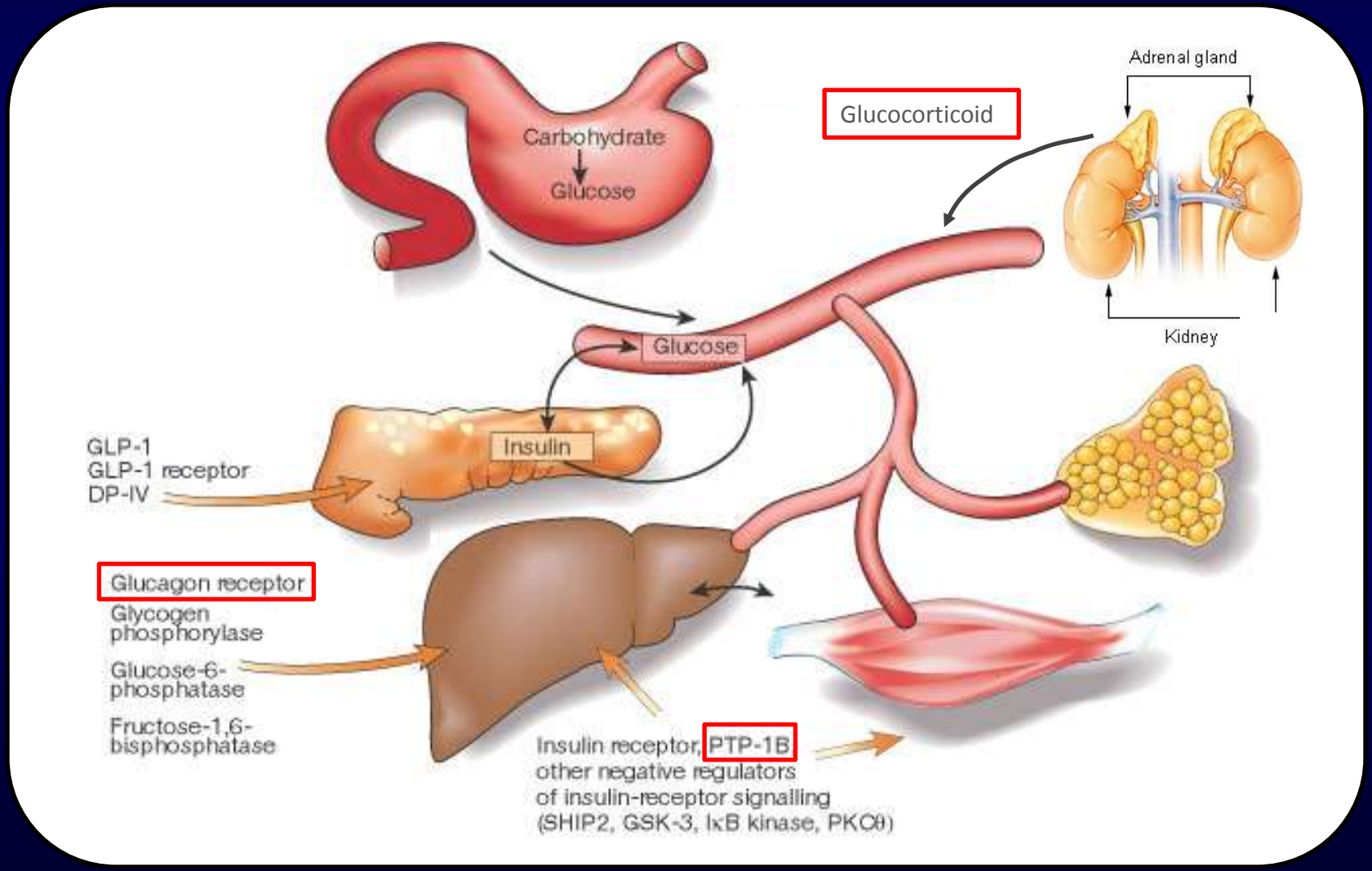
Limitations of Current Treatments for Patients with T2DM

- 5 classes of oral agents – 2 classes of SQ agents are recommended by ADA/EASD
- Limitations of currently available classes
  - Limited efficacy or durability: sulphonylurea (SU) agents, DPP-4 inhibitors
  - Hypoglycemia: SU agents, insulin
  - Weight gain: SU agents, PPARγ agents
  - GI side effects: metformin, GLP-1 agonists
  - Fluid retention: SU agents, PPARγ agents, insulin
- Conclusion: there is a need for new agents / new options

Need For More Powerful Glucose Lowering Therapies for T2DM

- The majority of patients with type 2 diabetes will fail on one or more therapies and progress in their disease
  - Significant number (>30%) patients fail treatment with insulin
- Addition of daily/weekly GLP-1 analogues to insulin results in combined HbA1c reductions of 0.8-1%
  - Significant number of patients remain uncontrolled

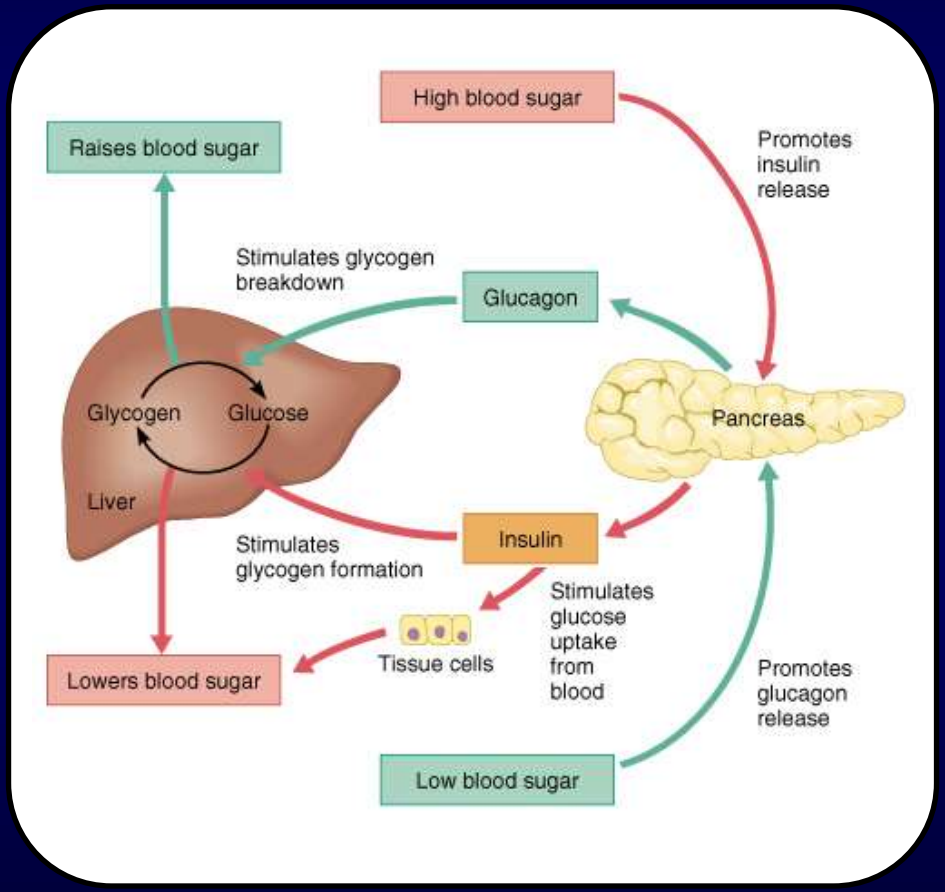
Type 2 Diabetes Patients Need Therapies That Directly Impact Mechanism of Disease



Glucagon Receptor (GCGR) A Validated Target for the Treatment of Diabetes

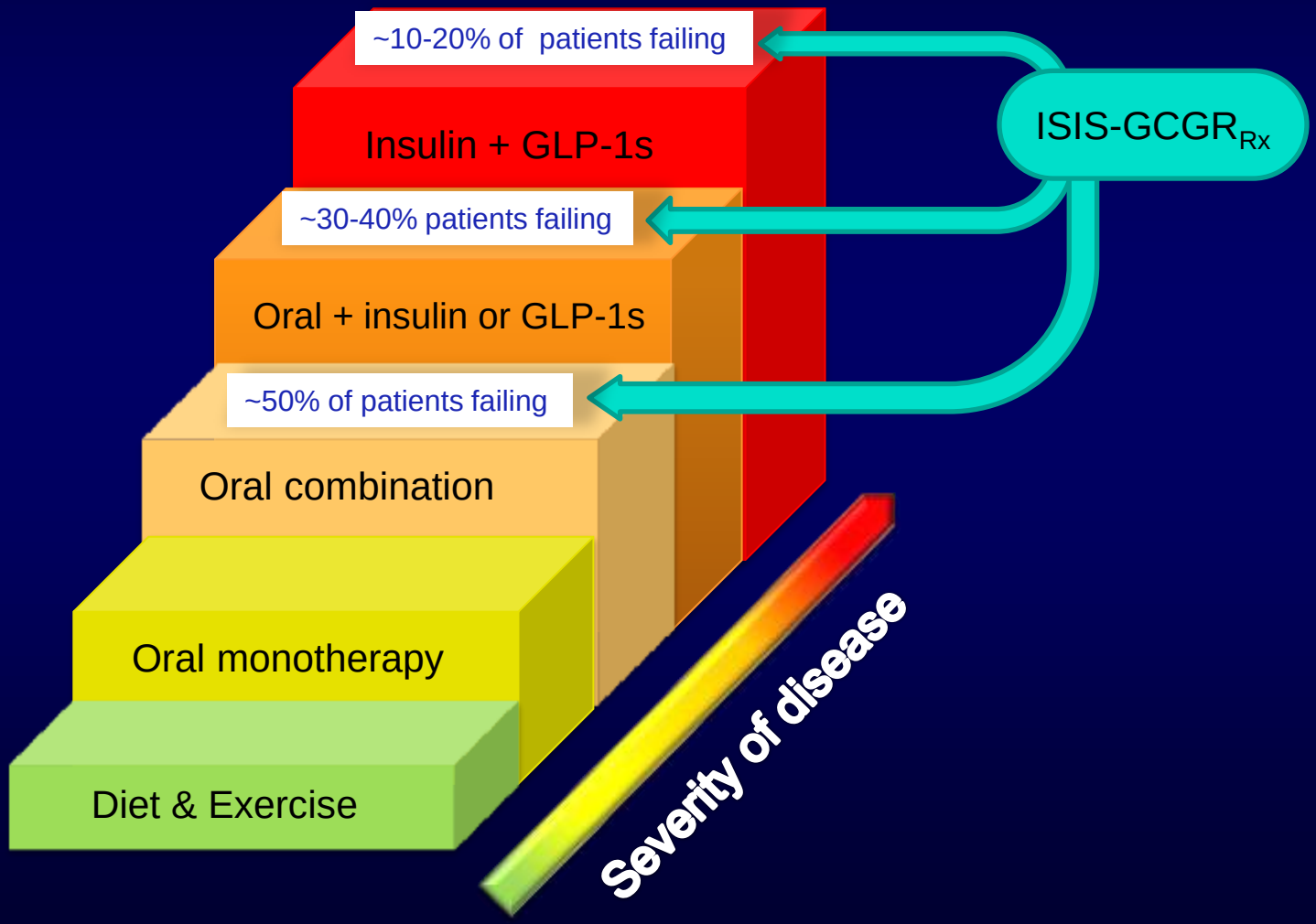
- Glucagon is a hormone that opposes the action of insulin
- Increased glucagon action leads to increased glucose production by the liver
- Glucagon receptor reduction in animal models produces dramatic reductions in glucose even in models of the most severe disease
- Small molecule inhibitors of GCGR have demonstrated glucose lowering effects in diabetic patients but also resulted in increases in LDL-cholesterol, body weight and blood pressure

Glucagon Receptor (GCGR) A Validated Target for the Treatment of Diabetes



- Effects of glucagon receptor inhibition:
  - Decreased glucose production by the liver
  - Increase in GLP-1, providing potential for pancreas sparing
  - GCGR-target inhibition has resulted in increases in liver enzymes

ISIS-GCGR$_{Rx}$ – Initial Target Populations



ISIS-GCGR$_{Rx}$ – Target Populations

Potential to be Used in Combination With Other Diabetes Treatments and Delay or Reduce the Need for Insulin and GLP-1 Analogs

- T2DM patients uncontrolled on oral anti-diabetic drugs (OADs)
  - Alternative to insulin or GLP-1 agonists
- T2DM patients uncontrolled on OADs plus insulin
  - Will reduce insulin requirements, thereby reducing side effects of insulin (hypoglycemia and weight gain)
  - Could reduce requirement of basal and/or meal-time insulin
- T2DM patients uncontrolled on OADs plus GLP-1 agonists
  - Could reduce dose of GLP-1 agonists, thereby reducing nausea, vomiting and GI-side effects
  - Could be added to daily or weekly GLP-1 agents
- T2DM patients on insulin plus GLP-1 agonists
  - Could be added to these therapies

ISIS-GCGR$_{Rx}$: Clinical Profile Observed To Date
Potential to Be Best In Class for Patients with Severe Diabetes

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ISIS-GCGR$_{Rx}$ Preclinical and Clinical Data and Plans

Dr. Sanjay Bhanot

VP Clinical Development & Translational Medicine
Isis Pharmaceuticals

Long History of Interest and Development Challenges in Targeting Glucagon Receptor

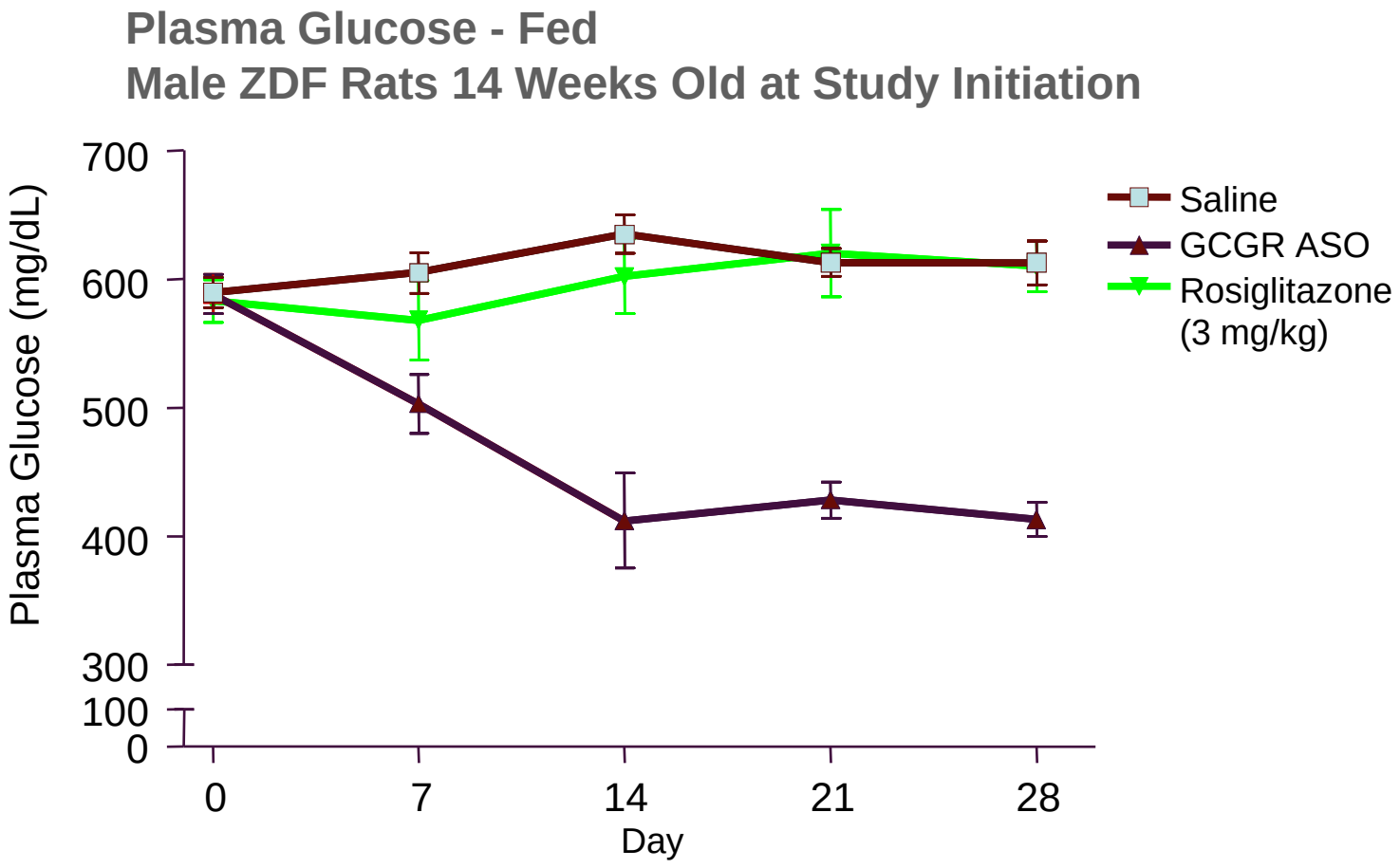
- **Small molecules achieved glucose control but associated with off-target side effects**
  - Increases in LDL-cholesterol
  - Increases in triglycerides
  - Increases in blood pressure
  - Increases in body weight
- **Mixed messages on KO results (some show normal animals, others show developmental defects)**
- **siRNAs with lipid nanoparticles increase lipid in the liver**

Glucagon Receptor Antisense Drug

Key Preclinical Observations

- **Reduced hepatic glucose production via potent inhibition of hepatic glucagon action with the added benefit of GLP-1 increases, which resulted in improved pancreatic insulin secretion**
- **Robust effects in very insulin resistant animals**
- **No fatty liver; expected transient increases in hepatic glycogen with no long-term increases; no changes in blood pressure or LDL cholesterol levels**
- **No hypoglycemia in rodents fasted up to 24 hours and in monkeys fasted up to 16 hours**
  - No effect on recovery from insulin-induced hypoglycemia in rodents
- **No alpha cell hyperplasia or pancreatic tumors with 6–month treatment in monkeys**

Antisense Inhibition of Glucagon Receptor Can Lower Plasma Glucose in Extremely Diabetic Animals in Which Rosiglitazone is Ineffective



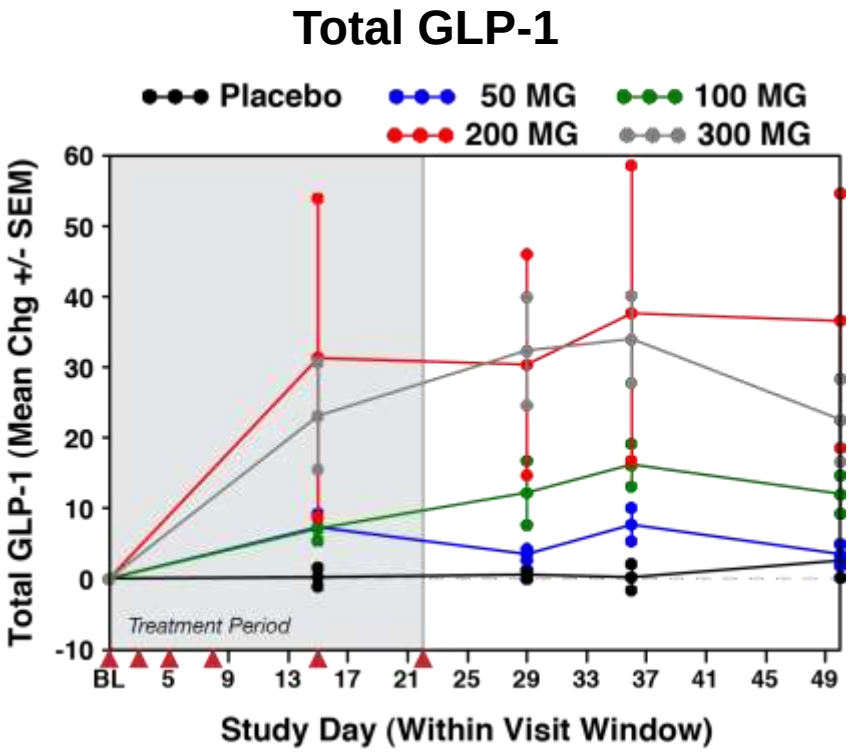
ISIS-GCGR$_{Rx}$ – Encouraging Activity

Results from Phase 1 Study

- No hypoglycemia
- Increased GLP-1 levels
- None of the small molecule caused off-target effects
  - No increases in LDL-cholesterol
  - No increases in triglycerides
  - No increases in blood pressure
  - No increases in body weight

ISIS-GCGR$_{Rx}$ Treatment Resulted in Increases in GLP-1 Levels

Results from Phase 1 Study

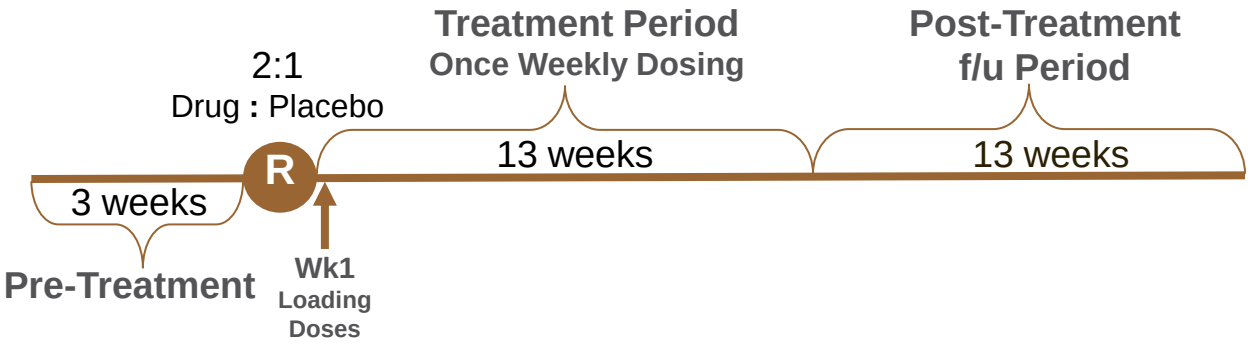


- **GLP-1 increases are higher than DPP-IV inhibitors:**
  - Provided confirmation of preclinical data
  - Potential to observe positive effects on pancreatic insulin secretion

ISIS-GCGR$_{Rx}$
13-week Phase 2 Study

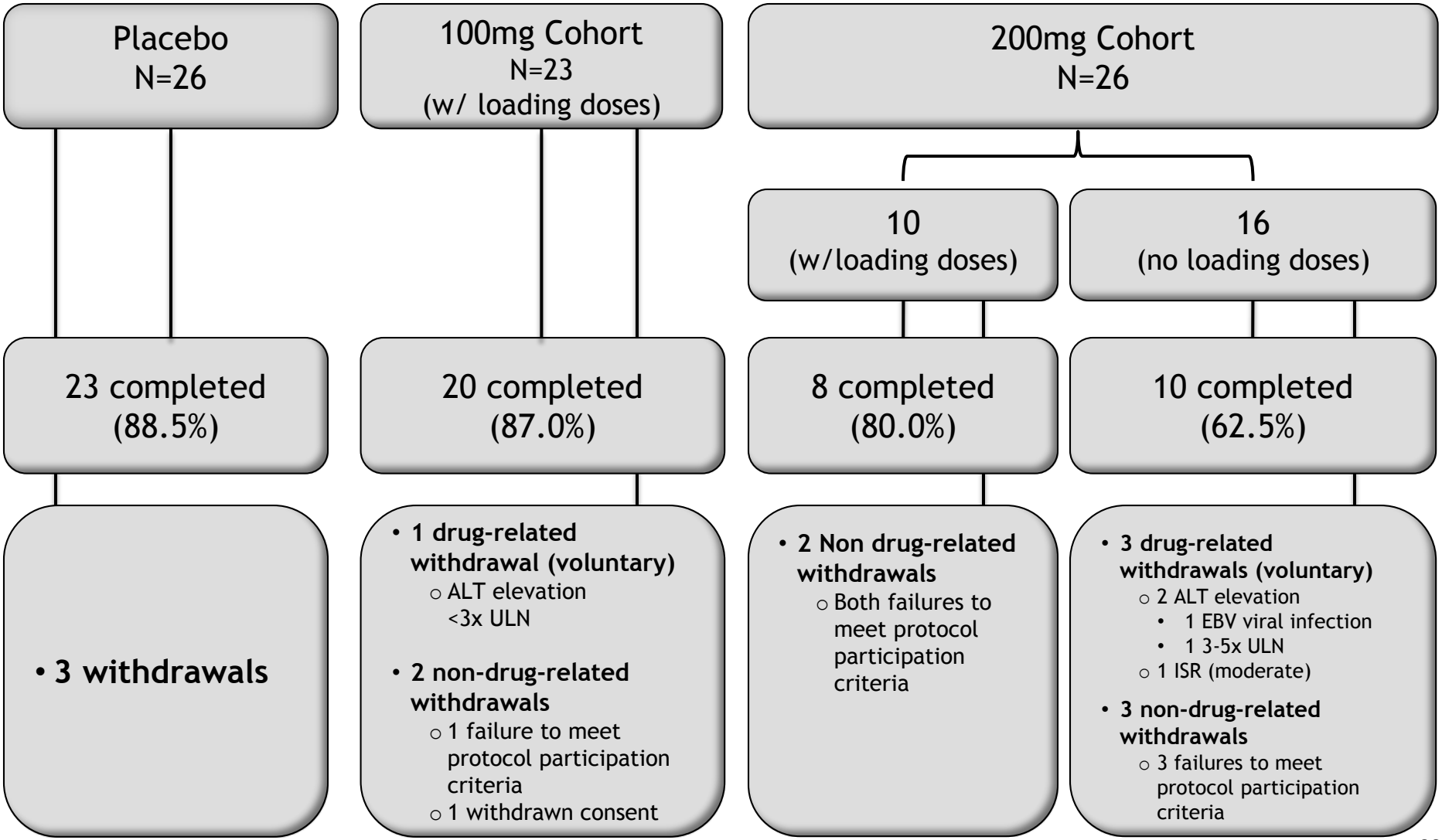
- **Randomized, double-blind, placebo-controlled study in patients with type 2 diabetes who are poorly controlled on stable metformin**
- **Objectives**
  - Evaluate effects on HbA1c and other measures of glucose control
  - Evaluate safety & tolerability
- **Endpoints – Fructosamine, HbA1c and other measures of glucose control**

Cohorts	n
100mg	36
200mg	39
200mg, no load	



ISIS-GCGR$_{Rx}$: Phase 2 Study Intent-to-treat (ITT) Patient Disposition

(N=75 Safety Population)



Baseline Characteristics - Mean (SD)

(N=75 Safety Population/ITT)

	Placebo (n=26)	100 mg ISIS-GCGR$_{Rx}$ (n=23)	200 mg ISIS-GCGR$_{Rx}$ (n=10)	200 mg (no load) ISIS-GCGR$_{Rx}$ (n=16)
Gender (M:F)	7:19	11:12	4:6	6:10
Age (yrs)	51.5 (8.7)	55.0 (10.2)	56.8 (7.7)	50.3 (10.5)
BMI (kg/m^2)	31.5 (4.2)	31.7 (5.1)	37.5 (6.4)	31.4 (4.8)
HbA1c (%)	8.6 (0.82)	8.6 (1.0)	9.1 (0.90)	8.8 (0.98)
Fructosamine (µmol/L)	324 (46.1)	326 (55.1)	308 (36.7)	324 (44.6)
FPG (mg/dL)	189 (41.0)	187 (67.5)	224 (47.1)	168 (32.6)
Insulin (µIU/mL)	15.4 (10.7)	16.8 (18.4)	19.4 (9.01)	12.9 (6.36)
C-Peptide (ng/mL)	3.2 (1.4)	3.3 (1.8)	4.0 (1.4)	2.8 (0.8)

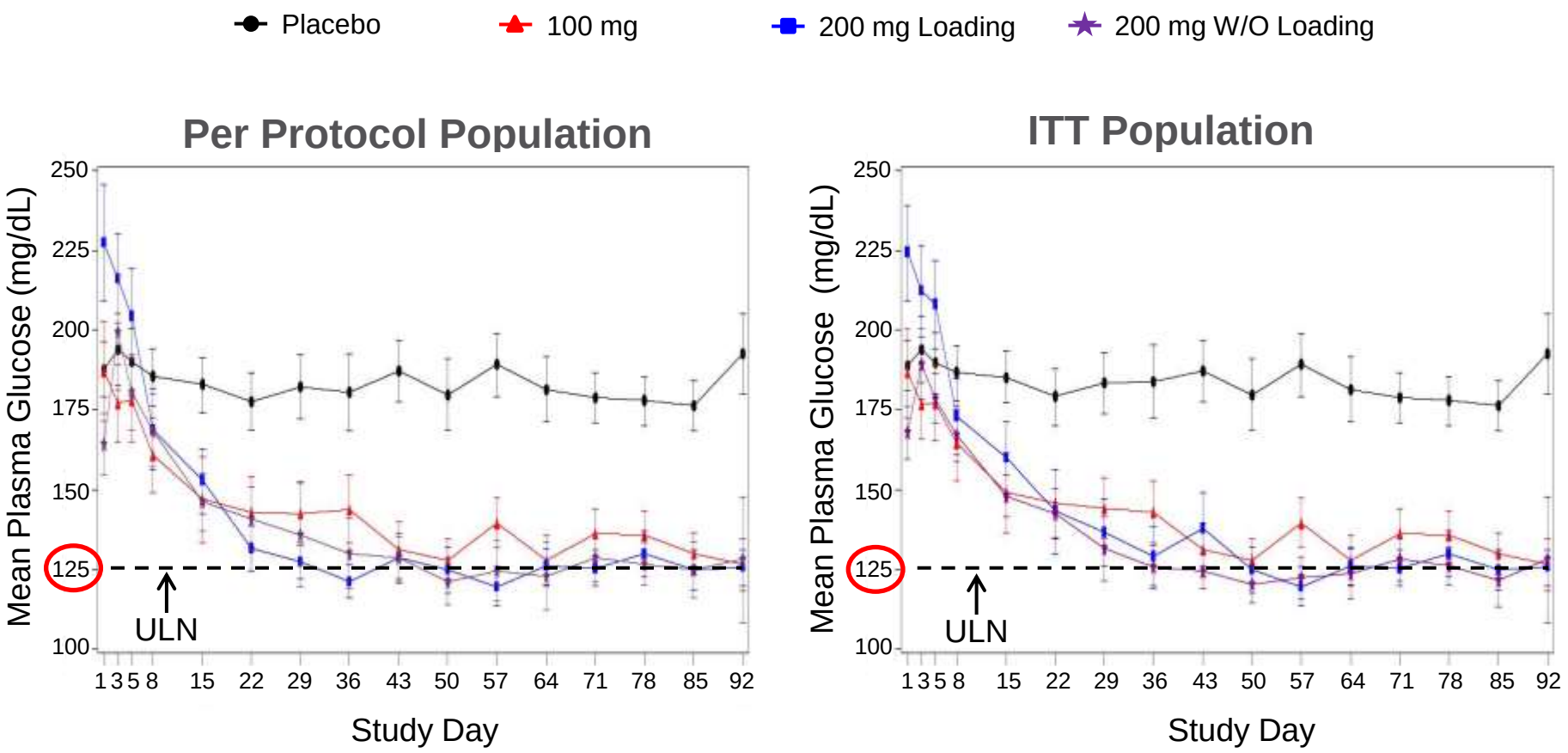
- **Analysis Populations:**
  - Full Analysis Set/Intent-to-treat (FAS/ITT) - all randomized patients who received at least 1 dose and had at least 1 post-dose efficacy measurement
  - Per Protocol (PP) - patients received at least 11 doses within 70 days (load) or 12 doses within 87 days (no load)

Patients Treated With ISIS-GCGR$_{Rx}$ Achieved Robust Improvements in Glycemic Control

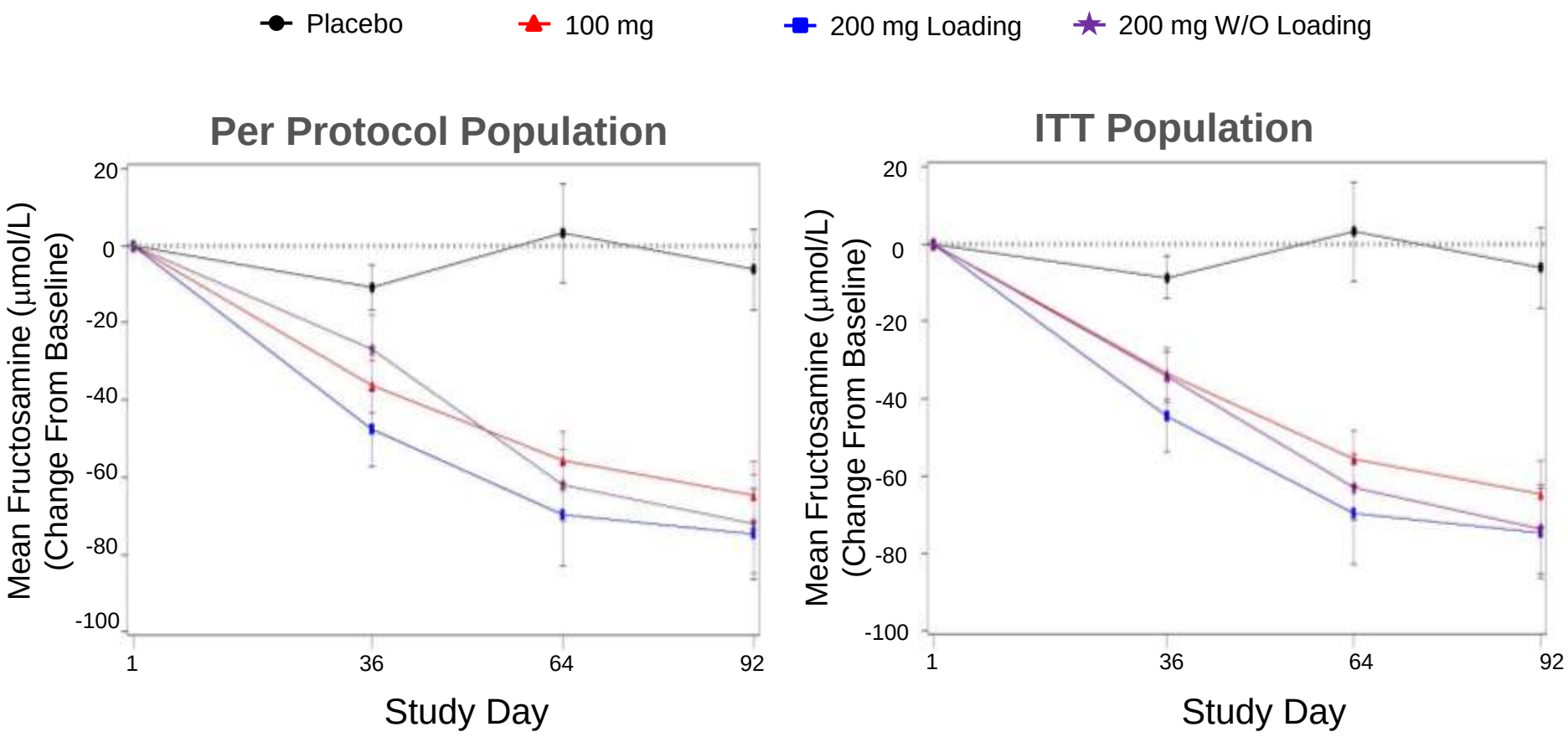
		ITT Population Mean (SEM)				Per Protocol Population Mean (SEM)			
		Placebo	100 mg	200 mg (load)	200 mg (no load)	Placebo	100 mg	200 mg (load)	200 mg (no load)
		N=26	N=23	N=10	N=16	N=24	N=21	N=8	N=9
HbA1c (%)	Baseline	8.61 (0.16)	8.62 (0.21)	9.13 (0.28)	8.83 (0.25)	8.60 (0.17)	8.55 (0.23)	9.10 (0.31)	8.80 (0.38)
	Change to Week 14	**-0.16** (0.23)	**-1.33*** ** (0.15)	**-1.95** ** (0.33)	**-1.56*** ** (0.18)	**-0.25** (0.24)	**-1.35*** ** (0.16)	**-2.25*** ** (0.33)	**-1.74** ** (0.27)
Fructosamine (µmol/L)	Baseline	324.2 (9.0)	326.4 (11.5)	307.6 (11.6)	323.9 (11.1)	323.2 (9.8)	324.4 (12.0)	309.9 (14.1)	324.9 (16.7)
	Change to Week 14	**-7.0** (9.3)	**-58.2*** ** (8.7)	**-59.8*** (13.9)	**-68.3*** ** (8.6)	**-7.6** (10.1)	**-62.3*** ** (8.8)	**-74.9** ** (11.7)	**-72.2** ** (12.7)
Total GLP-1 (pmol/L)	Baseline	5.35 (0.63)	6.83 (0.72)	8.16 (1.49)	4.76 (0.70)	5.09 (0.65)	6.51 (0.75)	7.65 (1.84)	4.55 (0.77)
	Change to Week 14	**-0.32** (0.50)	**9.86*** ** (1.41)	**16.20*** ** (3.42)	**20.01*** ** (2.96)	**-0.05** (0.51)	**9.13*** ** (1.35)	**19.89*** ** (2.98)	**19.97*** ** (3.50)

*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$, vs. Placebo

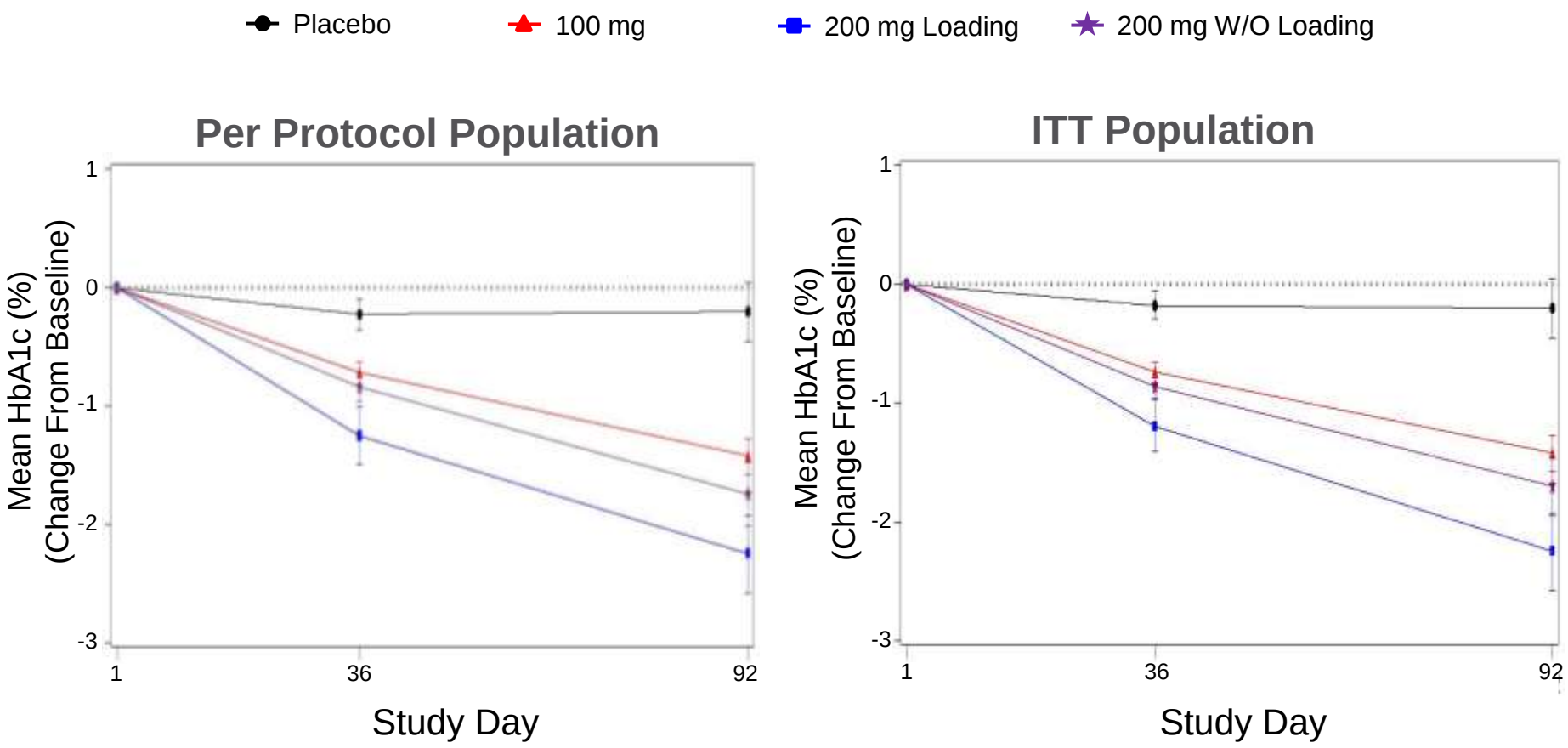
Patients Treated With ISIS-GCGR$_{Rx}$ Achieved Significant Reduction in Fasting Plasma Glucose Levels



Patients Treated With ISIS-GCGR$_{Rx}$ Achieved Significant Reduction in Fructosamine Levels



Patients Treated With ISIS-GCGR$_{Rx}$ Achieved Up to >2% Reduction in HbA1c After Only 13 Weeks



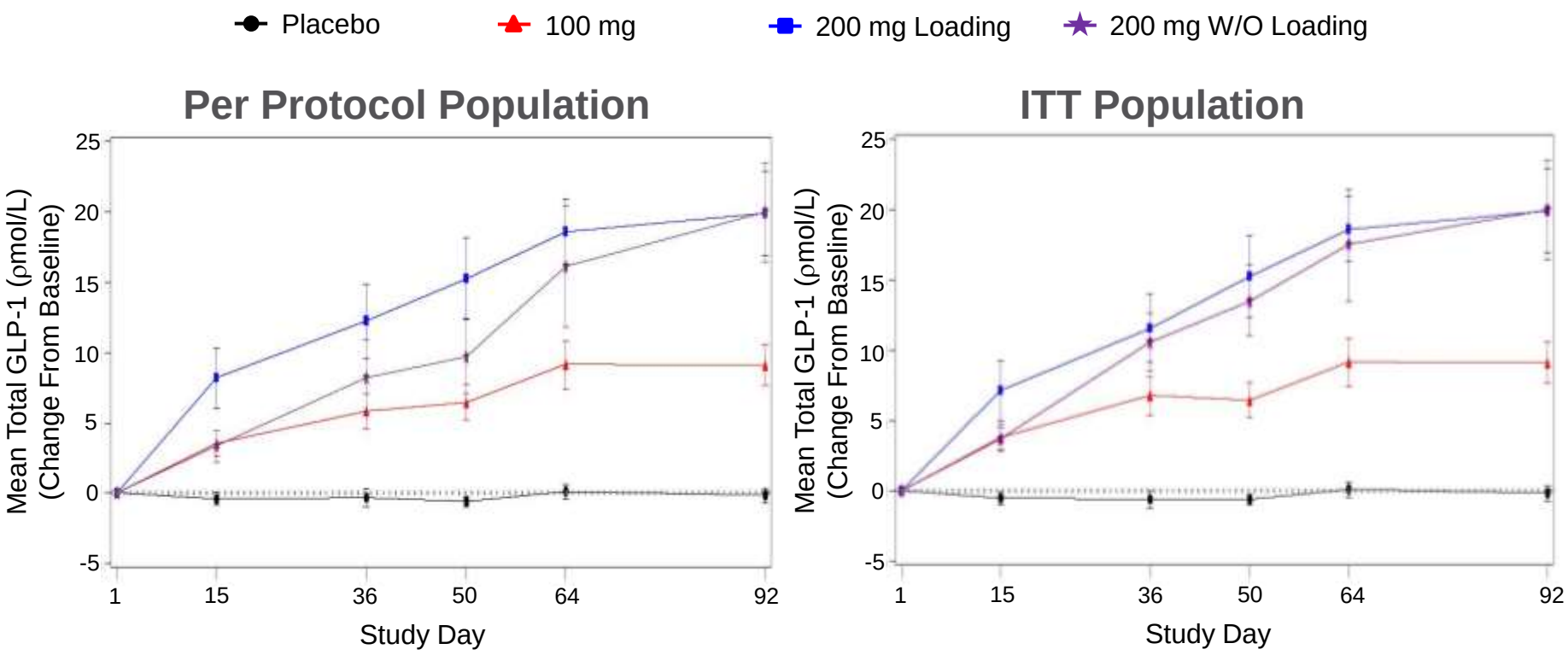
Large Proportion of Patients Reached HbA1c Levels ≤7% After Only 13 Weeks of ISIS-GCGR$_{Rx}$ Treatment

Per Protocol Analysis

		Placebo (n=24)	100 mg ISIS-GCGR$_{Rx}$ (n=21)	200 mg ISIS-GCGR$_{Rx}$ (n=8)	200 mg (no load) ISIS-GCGR$_{Rx}$ (n=9)
Day 92 (1 wk post last dose)	% (N)	12.5 (3)	47.6 (10)	75.0 (6)	55.6 (5)
	p-value vs placebo		0.010	0.002	0.020

- All ISIS-GCGR$_{Rx}$-treated patients demonstrated glucose reduction
- No ISIS-GCGR$_{Rx}$-treated patients discontinued due to uncontrolled hyperglycemia

Total GLP-1 Levels Are Increased in Patients Treated with ISIS-GCGR$_{Rx}$

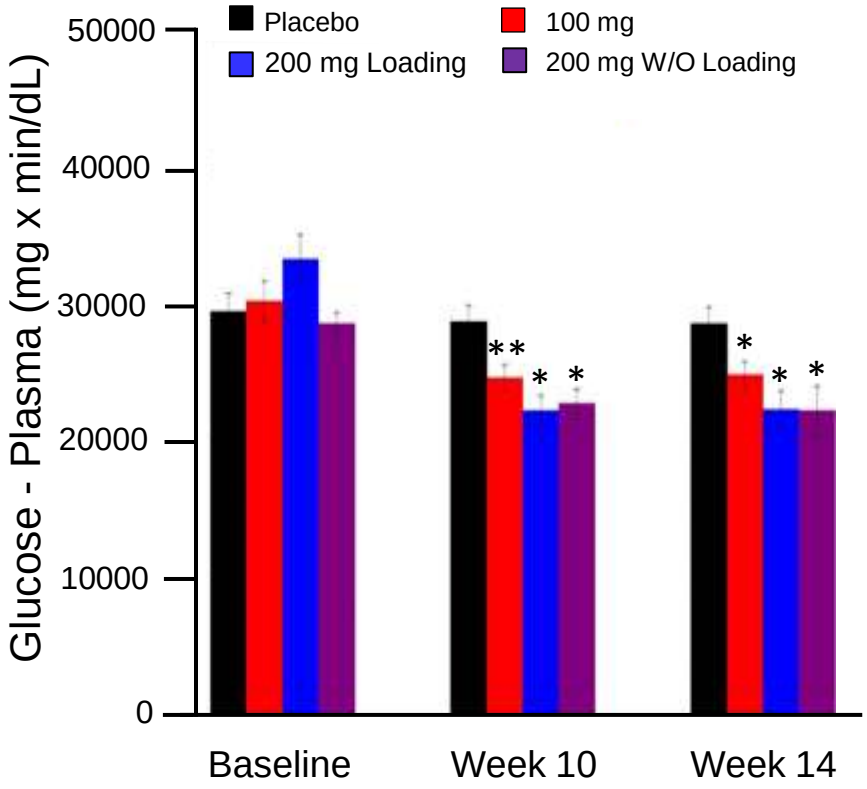


- DPP-IV inhibitors increase GLP-1 ~1.8 – 2.0 fold
- ISIS-GCGR$_{Rx}$ increases GLP-1 up to 4 fold
- ISIS-GCGR$_{Rx}$ produces greater GLP-1 increases than those observed with DPP-IV inhibitors without causing nausea and vomiting

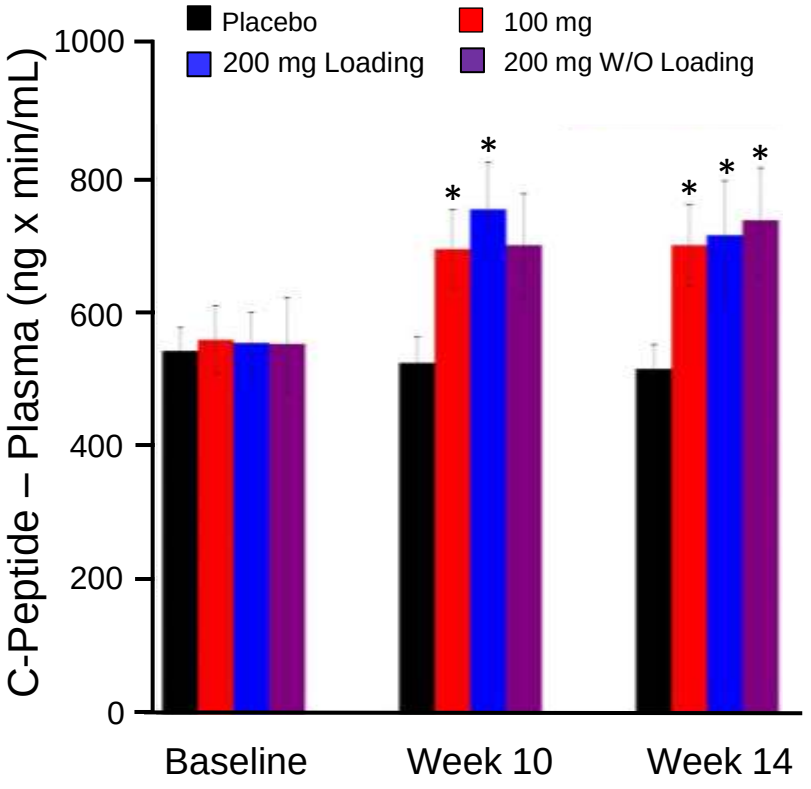
Improved Glucose Tolerance and Increased C-Peptide Levels Demonstrate GLP-1 Effect

(Per Protocol Population)

Improved Glucose Tolerance (Incremental AUC) during 2-hour OGTT



Increased C-Peptide (Incremental AUC) during 2-hour OGTT



**$p < 0.01$ vs. placebo

*$p < 0.05$ vs. placebo

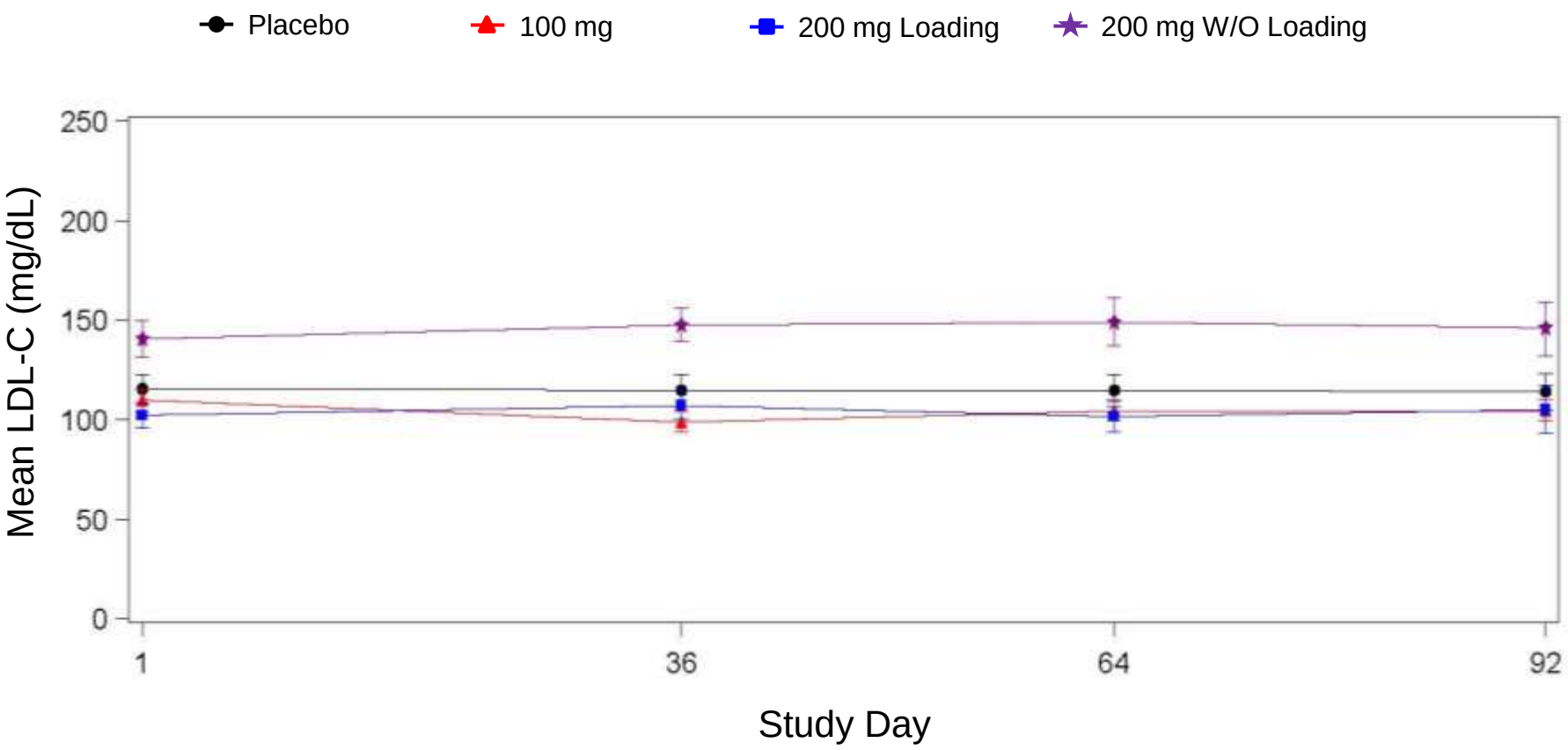
ISIS-GCGR$_{Rx}$ Treatment Was Well Tolerated and Produced Robust Improvements in Glycemic Parameters

Phase 2 Study Data – Safety and Tolerability

- **Well tolerated**
- **Antisense specificity of ISIS-GCGR$_{Rx}$ did not show the off-target effects seen with small molecules**
  - No clinically meaningful changes in LDL-cholesterol, triglycerides and blood pressure
  - No gain in body weight
- **No flu-like symptoms**
- **No nausea and vomiting (as observed with GLP-1 agonists)**
- **Infrequent, predominantly mild injection site reactions, resolved rapidly**
- **No cases of symptomatic hypoglycemia**

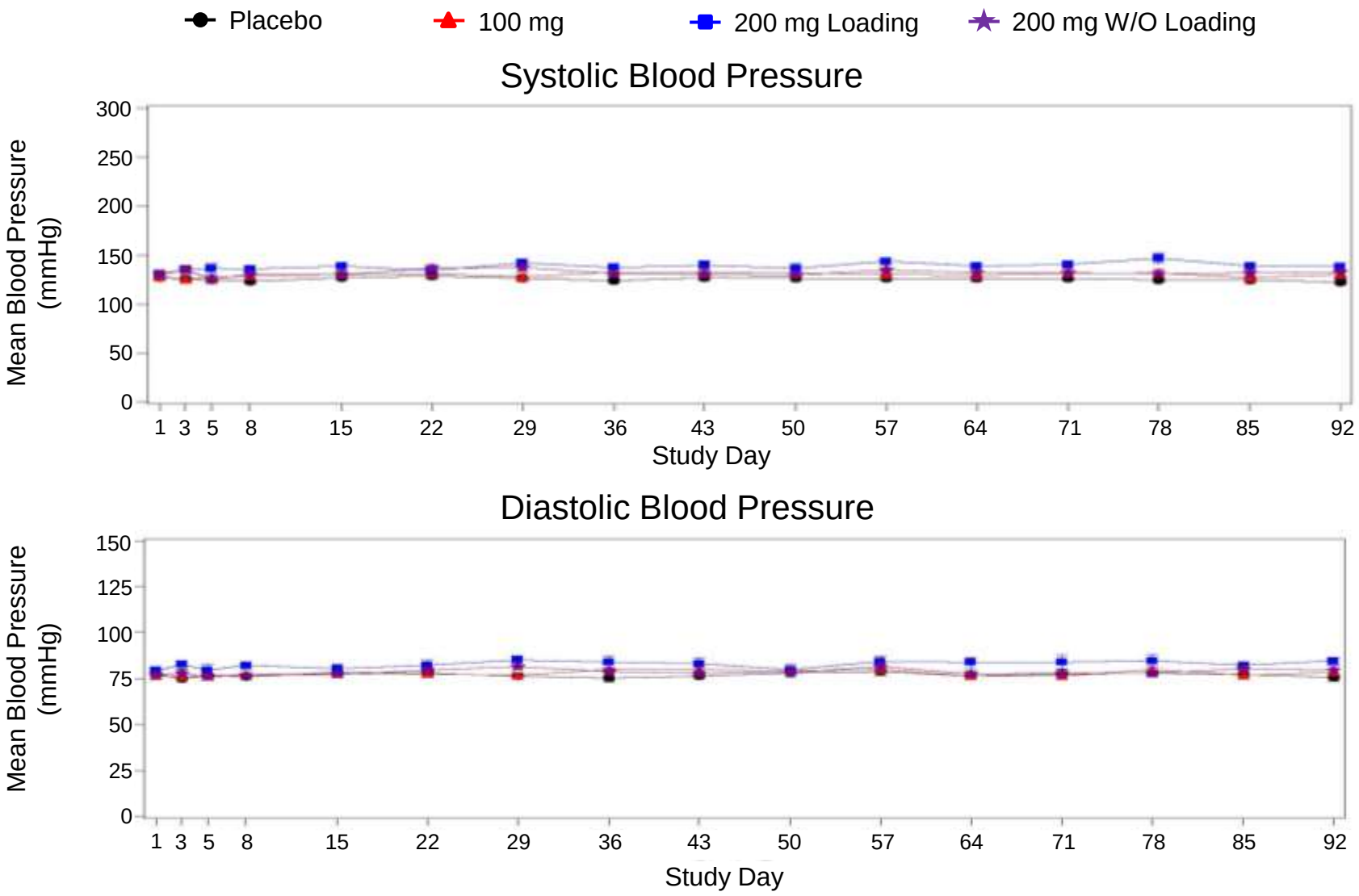
No Clinically Meaningful Changes in LDL-C in Patients Treated with ISIS-GCGR$_{Rx}$

(ITT Population)



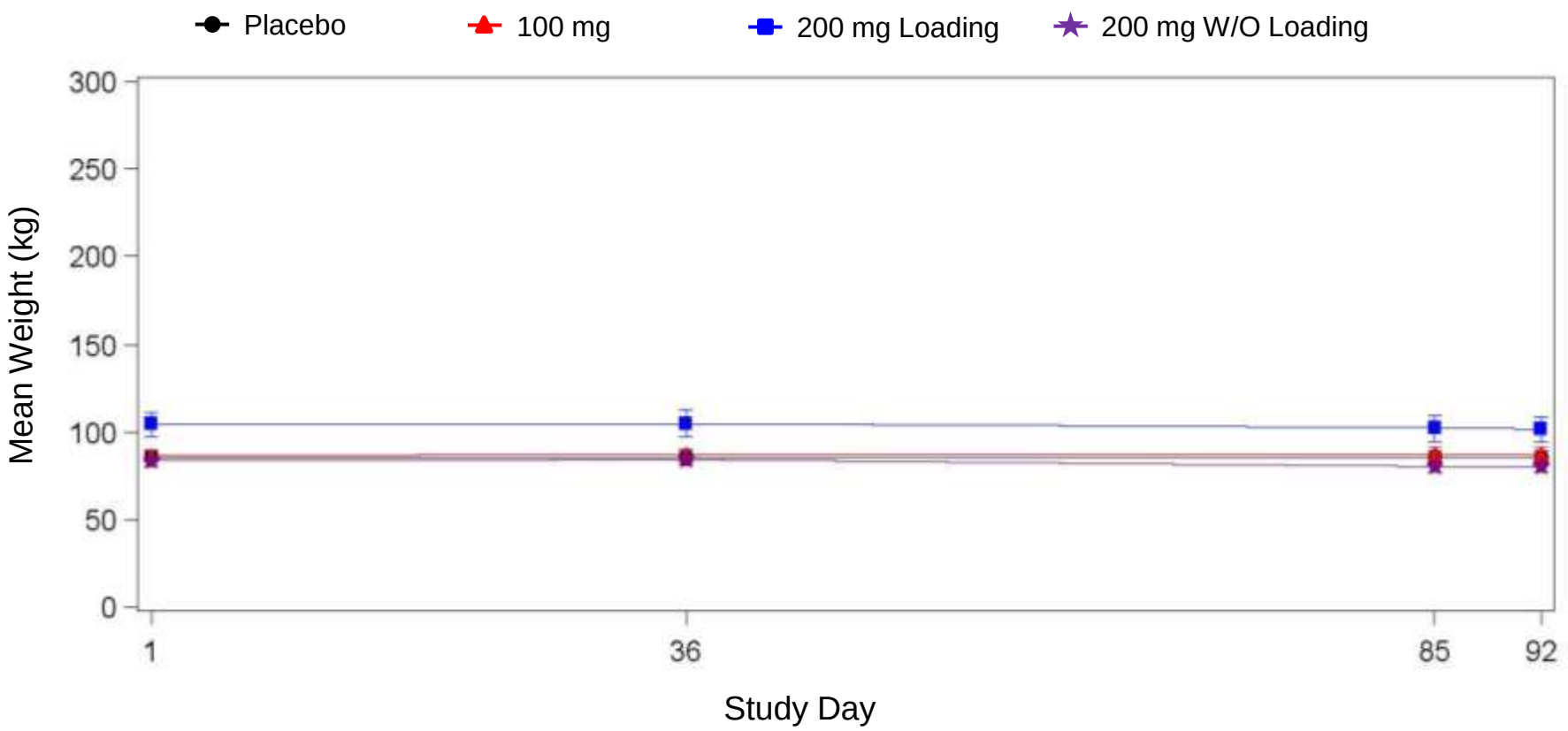
No Clinically Meaningful Changes in Blood Pressure in Patients Treated with ISIS-GCGR$_{Rx}$

(ITT Population)



No Clinically Meaningful Changes in Body Weight in Patients Treated with ISIS-GCGR$_{Rx}$

(ITT Population)



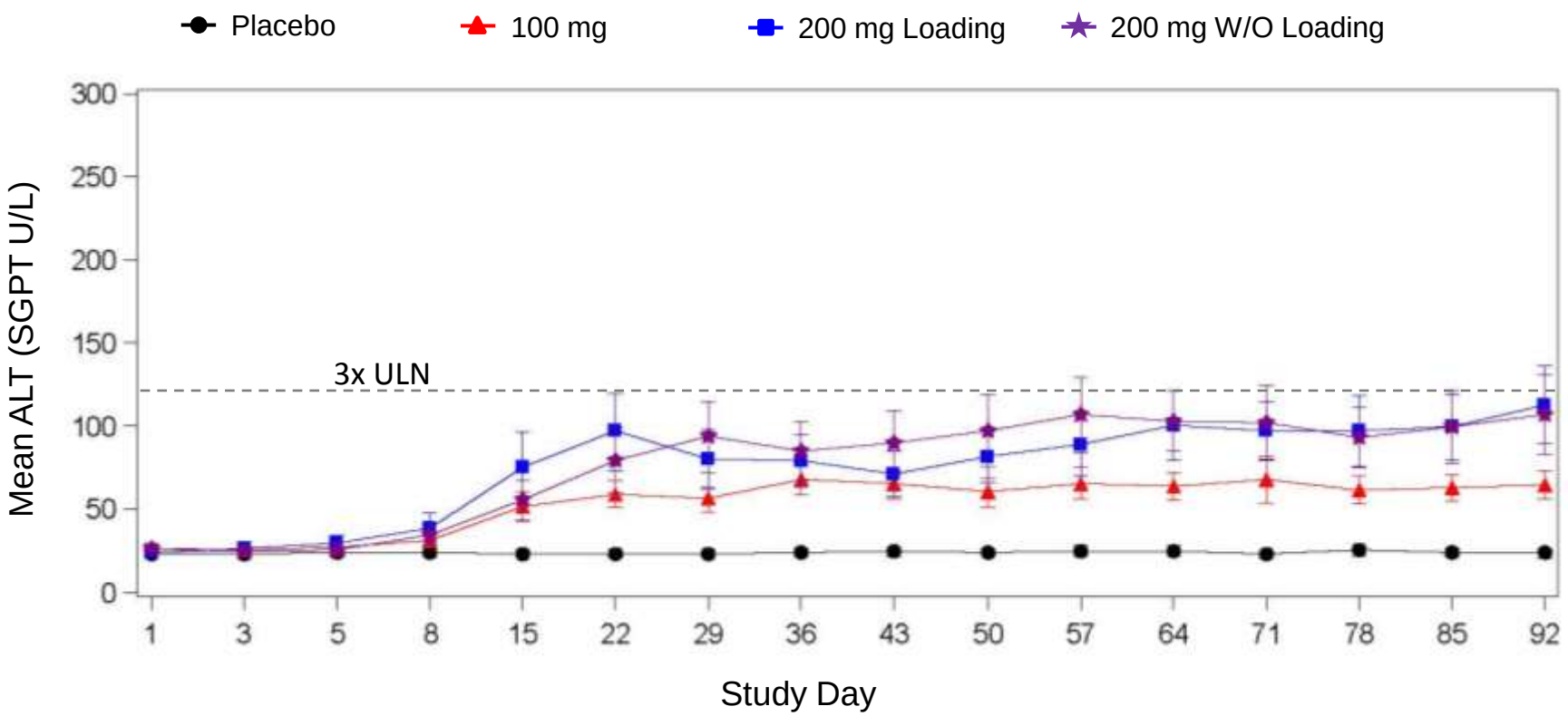
ISIS-GCGR$_{Rx}$ Treatment Produced Robust Improvements in Glycemic Parameters and Was Well Tolerated

Phase 2 Study Data – Safety and Tolerability

- **Target-related ALT elevations consistent with the pharmacology of glucagon receptor inhibition and similar to those observed with small molecule glucagon inhibitors**
  - No ALT elevations >8x ULN
    - Mean ALT elevation in 100 mg cohort was 1.6x ULN
    - Mean ALT elevation in 200 mg cohort was 2.7x ULN
  - Liver enzyme elevations declined after dosing discontinued
  - No increases in bilirubin; no Hy's Law cases
  - No effect on liver function
  - No stopping rules met

Mean ALT Levels Remain Below 3xULN in Patients Treated with ISIS-GCGR$_{Rx}$

(ITT Population)



Data Strongly Support Developing ISIS-GCGR$_{Rx}$:

Potential to Be Best in Class for Patients with Severe Diabetes

- Robust and long-lasting effects on glucose control observed
- Potential for potent inhibition of hepatic glucagon action with the added benefit of GLP-1 increases
- Potential to have greater glucose reduction than small molecules by directly reducing production of the receptor
- In clinical trials to date, no clinically meaningful effects observed on LDL, blood pressure and body weight, and no nausea or vomiting
- Significant dose-dependent reductions in HbA1c support identification of optimal dose and schedule to achieve glucose control with minimal glucagon receptor-related liver enzyme elevations

ISIS-GCGR$_{Rx}$
Next Steps in Development

- **Optimize dose and dosing schedule**
- **Complete long-term toxicology studies to support long-term clinical studies**
- **Continue discussion with partners**
  - Strong partner interest

ISIS-PTP1B$_{Rx}$ and ISIS-GCCR$_{Rx}$

Brett Monia

SVP, Antisense Drug Discovery
Isis Pharmaceuticals

ISIS-PTP1B$_{Rx}$: Toward A Safer, More Effective Insulin Sensitizer

- **Other insulin sensitizers, such as glitazones, are transcriptional activators with limitations due to their side effects**
  - Significant unmet need for a safe and effective insulin sensitizer
- **ISIS-PTP1B$_{Rx}$ selectively targets protein tyrosine phosphatase 1B (PTP-1B), a negative regulator of insulin action, to enhance cellular insulin response**
- **Antisense inhibition of PTP-1B has been shown to improve glycemic control in both preclinical and in clinical studies**

ISIS-PTP1B$_{Rx}$: Potential to Have a Strong Profile as a Novel and Safe Insulin Sensitizer

Drug	Glucose reduction	No Hypo-glycemia	Lipids reduction	Body Weight reduction	No GI Side Effects	Insulin Sensitivity & Adipocytokines	No Target Toxicity
PTP-1B Antisense[1]	Yes	Yes	Yes	Yes	Yes	Yes, adiponectin increase	Yes
PPAR-γ[2]	Yes	No (Minimal)	No or Minimal	No, wt gain	Yes	Yes	No (Cardiac, BW gain & bone loss)

[1] Based on preclinical data and preliminary clinical data

[2] Based on published data including label claims

PTP-1B Inhibition – Encouraging Profile

Preclinical and Clinical Profile

Parameter	Result
Insulin	↓
Glycemic control	Improved
Hypoglycemia	No
HOMA-insulin resistance	↓
Body weight	↓
Adiponectin	↑
Lipids	↓
Potency	↑

Subjects treated with ISIS-PTP1B$_{Rx}$ experienced:

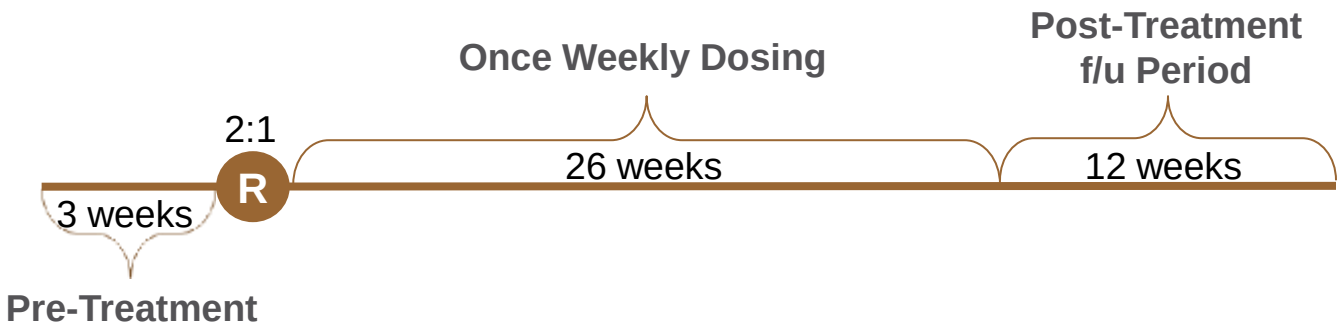
- **Lower insulin levels and reduced insulin resistance (as measured by HOMA-IR)**
- **Increased plasma adiponectin, a biomarker associated with weight loss**
- **No hypoglycemia**

ISIS-PTP1B$_{Rx}$ Phase 2 (ongoing)

Six-Month Study, Data Planned YE 2014

- **Randomized double-blind placebo-controlled study in obese patients with type 2 diabetes who are poorly controlled on metformin or metformin + sulfonylurea**
- **Objectives:**
  - Evaluate efficacy in various parameters of glucose control, including HbA1c
  - Evaluate safety and tolerability
- **Enrollment complete, data planned for 2H 2014**

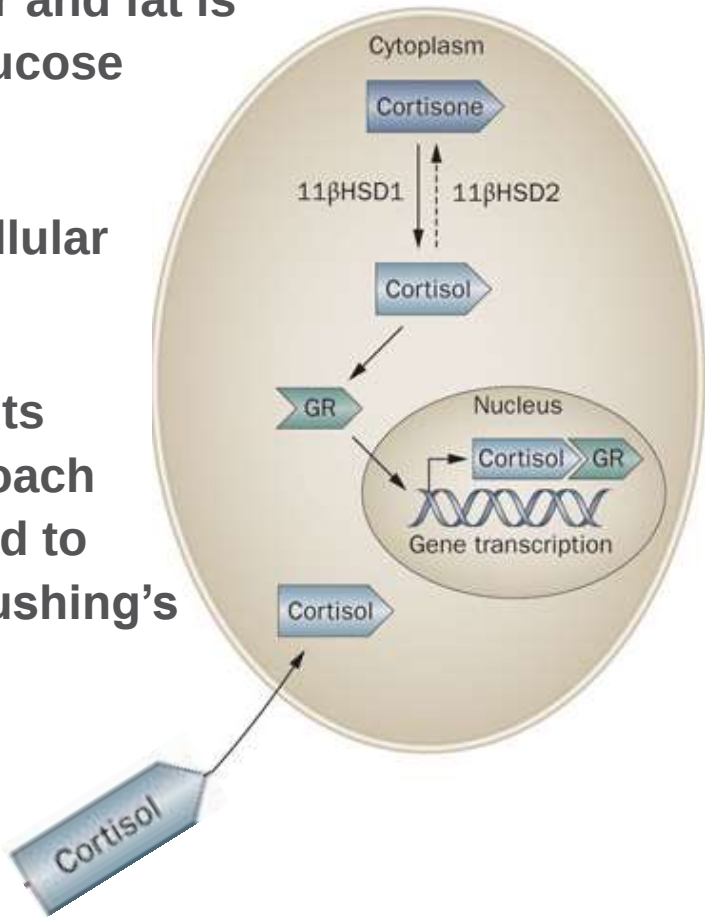
Cohorts	n
200mg	75



Tissue-specific Reduction of the Glucocorticoid Receptor

A Unique Therapeutic Target for the Treatment of Diabetes

- Excessive glucocorticoids (GC) action in liver and fat is involved in obesity, insulin resistance and glucose intolerance
- Glucocorticoid receptor (GCCR) is an intracellular receptor that mediates the action of GCs
- Attenuation of peripheral GC action through its receptor is a very attractive therapeutic approach for type 2 diabetes and other disorders related to excessive and chronic steroid action (e.g., Cushing's disease)



Tissue-specific Reduction of the Glucocorticoid Receptor

A Unique Therapeutic Strategy for the Treatment of Diabetes

- **Small molecule inhibitors of GCCR have failed or have had limited utility**
  - GCCR inhibition in the brain can cause increases in ACTH, adrenal insufficiency, hypokalemia and blood pressure
- **ISIS-GCCR$_{Rx}$ has the potential to be best in class by taking advantage of distribution of antisense drugs**
  - Inhibits GCCR in liver and fat *without crossing the blood-brain barrier*
  - Provides therapeutic benefits of inhibiting GC action without target-associated central nervous system side effects

ISIS-GCCR$_{Rx}$ – Encouraging Activity and Safety Profile

Results from Phase 1 Studies

Parameter	Result
Triglycerides	Decreased
Total cholesterol	Decreased
LDL-cholesterol	Decreased
VLDL-cholesterol	Decreased
ACTH	No change
Aldosterone	No change
Renin	No change
Angiotensin II	No change
Blood pressure	No change
Hypoglycemia	No

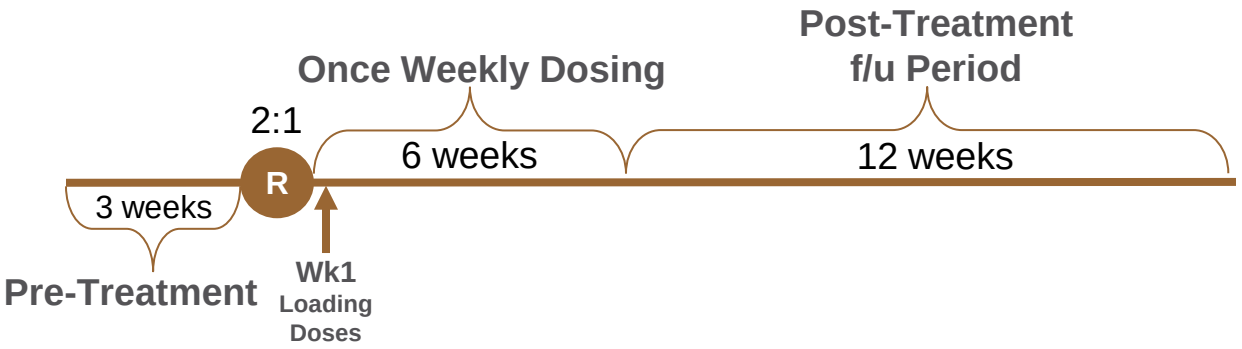
- Positive effects on lipid profile, consistent with preclinical data
- No evidence of GCCR antagonism in brain or other tissues outside of liver and adipose
- No change in blood pressure
- Observed safety profile suggests ISIS-GCCR$_{Rx}$ has not shown the limitations observed with small molecule inhibitors of GCCR

ISIS-GCCR$_{Rx}$ Phase 2 (ongoing)

Six-Week Study, Data Planned for Late 2014/Early 2015

- **Randomized double-blind placebo controlled study in patients with type 2 diabetes who are poorly controlled on metformin**
- **Objectives:**
  - Evaluate short-term measures of glycemic control
  - Evaluate the safety and tolerability
    - Changes in markers of GCCR antagonism in the brain
    - Hypoglycemia
  - Evaluate effects on lipid profile
  - Provide supportive data to move into longer-term studies
- **Data planned for late 2014/early 2015**

Cohorts	n
210mg	40



ISIS-GCCR$_{Rx}$
Potential Opportunities and Next Steps Toward Market

- **Near Term, High Value Patient Populations**
  - Cushing's Disease – orphan indication
  - Subset of dyslipidemic type 2 diabetes patients most likely to benefit from reduced glucocorticoid drive
- **Next Steps**
  - Initiate Phase 2 study in patients with Cushing's Disease - 2H 2014
  - Complete Phase 2 study and report data in patients with type 2 diabetes – late 2014/early 2015

ISIS-GCGR$_{Rx}$: Partnering Opportunity and Upcoming Milestones

B. Lynne Parshall
COO
Isis Pharmaceuticals

Isis' Flexible Development and Partnership Strategy

Maximizes Value, Minimizes Risk and Decreases Time to Market

Partner Early

- Significant technical or target risk
- Complex, difficult, expensive Phase 2 program
- Challenging endpoints
- Expertise from partner could provide increased likelihood of success

License After POC

- Complex, expensive Phase 3 development
- Straightforward, effective Phase 2 program with definitive endpoints
- Multiple indications
- Large patient population
- Large marketing and sales effort

Keep Longer

- Clear Phase 2, Phase 3 development path
- Low to moderate total development costs
- Potential for initial rare disease opportunity
- Consistent with Isis intellectual franchises

Examples:

Partner Early	License After POC	Keep Longer
ISIS-SMN$_{Rx}$ (biogen idec.)	**ISIS-GCGR$_{Rx}$**	**ISIS-APOCIII$_{Rx}$**
ISIS-STAT3$_{Rx}$	**ISIS-FXI$_{Rx}$**	**ISIS-PKK$_{Rx}$**
ISIS-AR$_{Rx}$ (AstraZeneca)	**ISIS-PTP1B$_{Rx}$**	**ISIS-APO(a)$_{Rx}$**
	ISIS-GCCR$_{Rx}$	

Isis' Type 2 Diabetes Pipeline

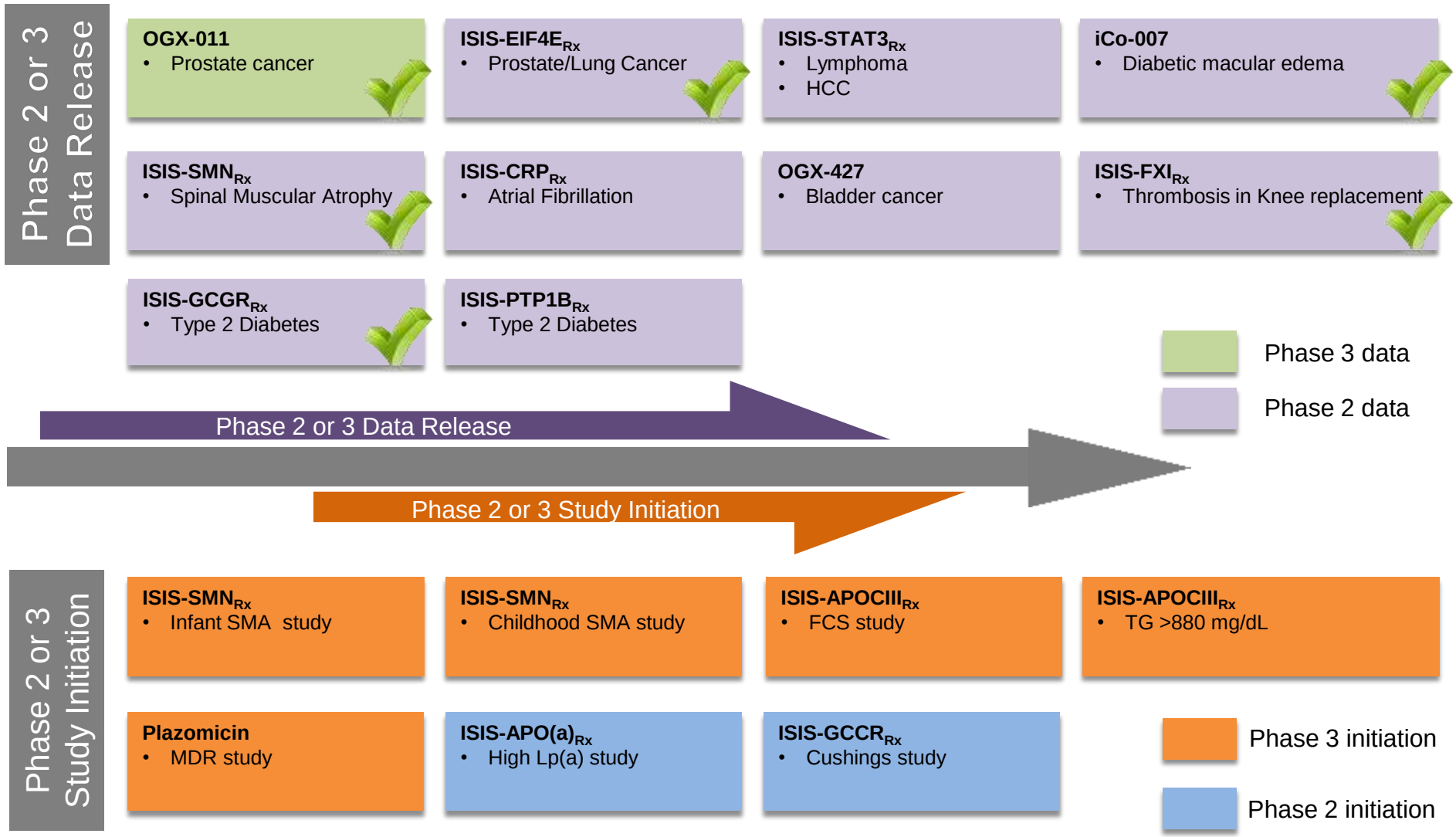
Three Phase 2 Study Readouts in 2014/2015

DRUG	INDICATION	CURRENT STATUS	NEXT STEP
ISIS-GCGR$_{Rx}$	Diabetes	Phase 2 study ongoing	Phase 2 data 2014
ISIS-PTP1B$_{Rx}$	Diabetes	Phase 2 study ongoing	Phase 2 data YE2014
ISIS-GCCR$_{Rx}$	Diabetes	Phase 2 study ongoing	Phase 2 data 2014/2015

- Strong partnership interest for Isis metabolic programs
- Isis' metabolic drugs specifically reduce molecular targets, many of which are undruggable or have been difficult to target with small molecules
- Each drug in the franchise focuses on a unique therapeutic opportunity and is complementary

Advancing the Pipeline

Multiple Phase 2 and 3 Data Read Outs & Planned Study Initiations in 2014



ISIS-GCGR$_{Rx}$: Clinical Profile Observed To Date

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Diabetes Program Review

Q&A