Lixisenatide and iGlarLixi Type 2 Diabetes Mellitus

Endocrinologic and Metabolic Drugs

Advisory Committee

May 25, 2016

Introduction

Paul Chew, MD

Senior Vice President, Research and Development

Sanofi

Seeking Approval of Lixisenatide and iGlarLixi for Treatment of Type 2 Diabetes

- Presentation on Lixisenatide and iGlarLixi
- iGlarLixi – combination of two products
  - Lantus® – insulin glargine
  - Lixisenatide – GLP-1 agonist

Lantus Background

- 2000 – Lantus approved in US / Europe
  - Global standard for long-acting basal insulins
  - 15+ years of worldwide safety
  - CV safety in >6,000 Lantus-treated patients (ORIGIN[1] study)
- Insulin risk of weight gain / hypoglycemia

1. ORIGIN Trial Investigators (NEJM 2012)

Lixisenatide Developed to Improve Glycemic Control in Adults with Type 2 Diabetes

- Marketing authorization in Europe – 2013
  - Subsequently approved worldwide
- Lixisenatide NDA submitted – 2015
  - Long-term cardiovascular outcomes study (ELIXA[1])
- CV safety shown for both Lantus and Lixisenatide

1. ELIXA Trial Investigators (2015)

Proposed Lixisenatide Indication

- Lixisenatide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus.

iGlarLixi is Novel Approach to Controlling Blood Glucose

- Achieve target HbA_{1c}
  - Without increasing risk of hypoglycemia / weight gain
  - Better GI tolerability
- Addresses both FPG and PPG with one injection
- 2 fixed ratios for wide range of patients with diabetes
- Patients needing intensification beyond OADs or basal insulin
- Allows administration of Lixisenatide between 5 and 20 µg
  - Same titration as Lantus

Proposed Indication iGlarLixi

- Insulin glargine / Lixisenatide fixed ratio combination is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both insulin glargine and Lixisenatide is appropriate.

Agenda

Need for New Treatment Options	**Neil Skolnik, MD** Temple University School of Medicine
MoA of Lixisenatide and iGlarLixi	**John Newton, PhD** VP Pharmacokinetics, Dynamics, Sanofi
Efficacy of Lixisenatide and iGlarLixi	**Rachele Berria, MD, PhD** VP Head Diabetes Medical Unit, Sanofi
Safety of Lixisenatide and iGlarLixi	**Kristen Sharma, MD** VP Global Diabetes and CV Pharmacovigilance Unit, Sanofi
FDA Points to Consider	**René Belder, MD** Global Project Head, Sanofi
Benefit Risk	**Luigi Meneghini, MD** University of Texas Southwestern Medical Center

Additional Experts

Elizabeth Andrews, PhD	RTI Health Solutions Epidemiologist
Juan Frias, MD	National Research Institute Endocrinologist - iGlarLixi Investigator
Hertzel Gerstein, MD	McMaster University Endocrinologist
Allen Kaplan, MD	Medical University of South Carolina Allergist
Gary Koch, PhD	University of North Carolina Biostatistician

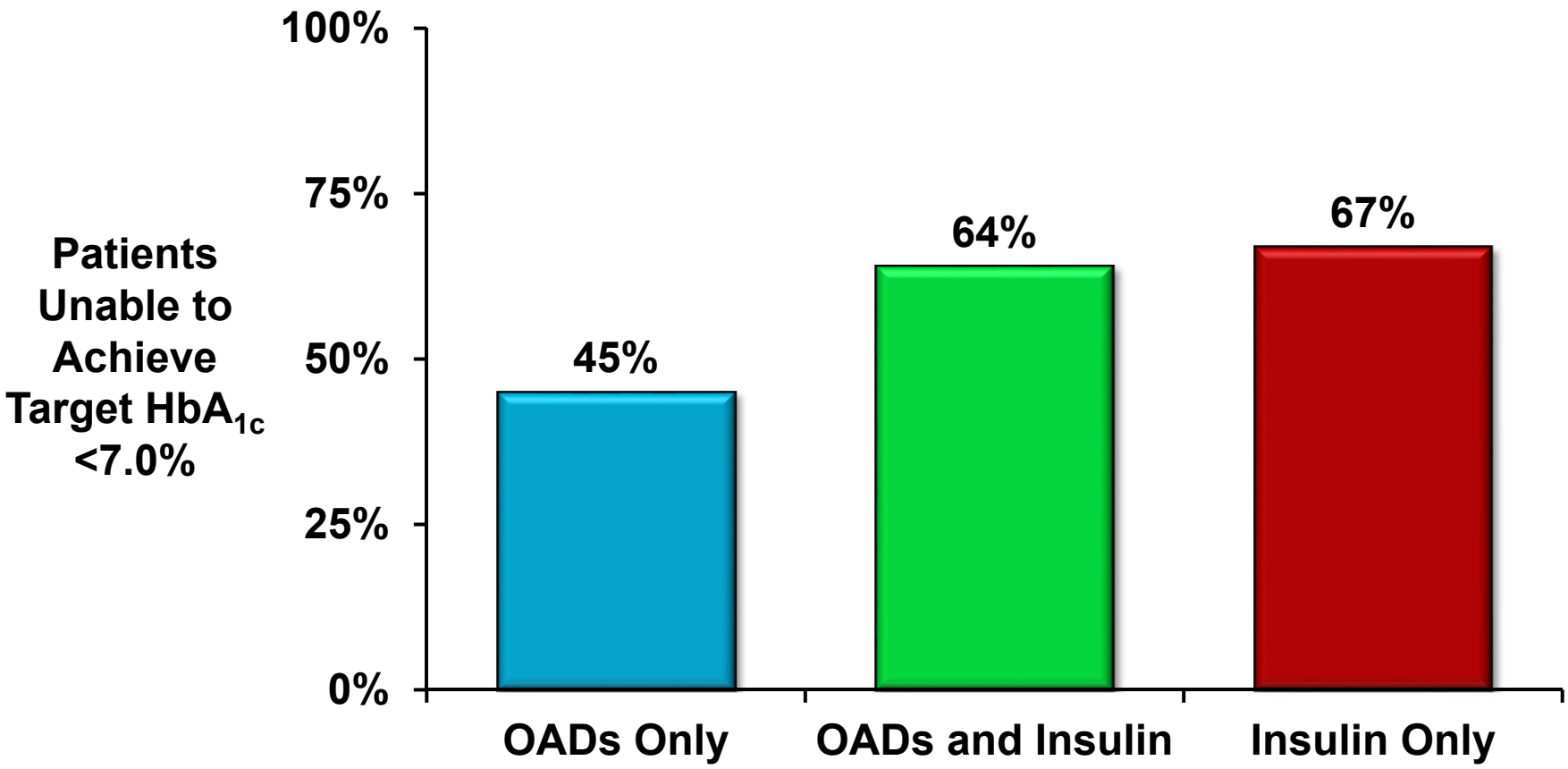
Need for New Treatment Options

Neil Skolnik, MD

Professor of Family and Community Medicine

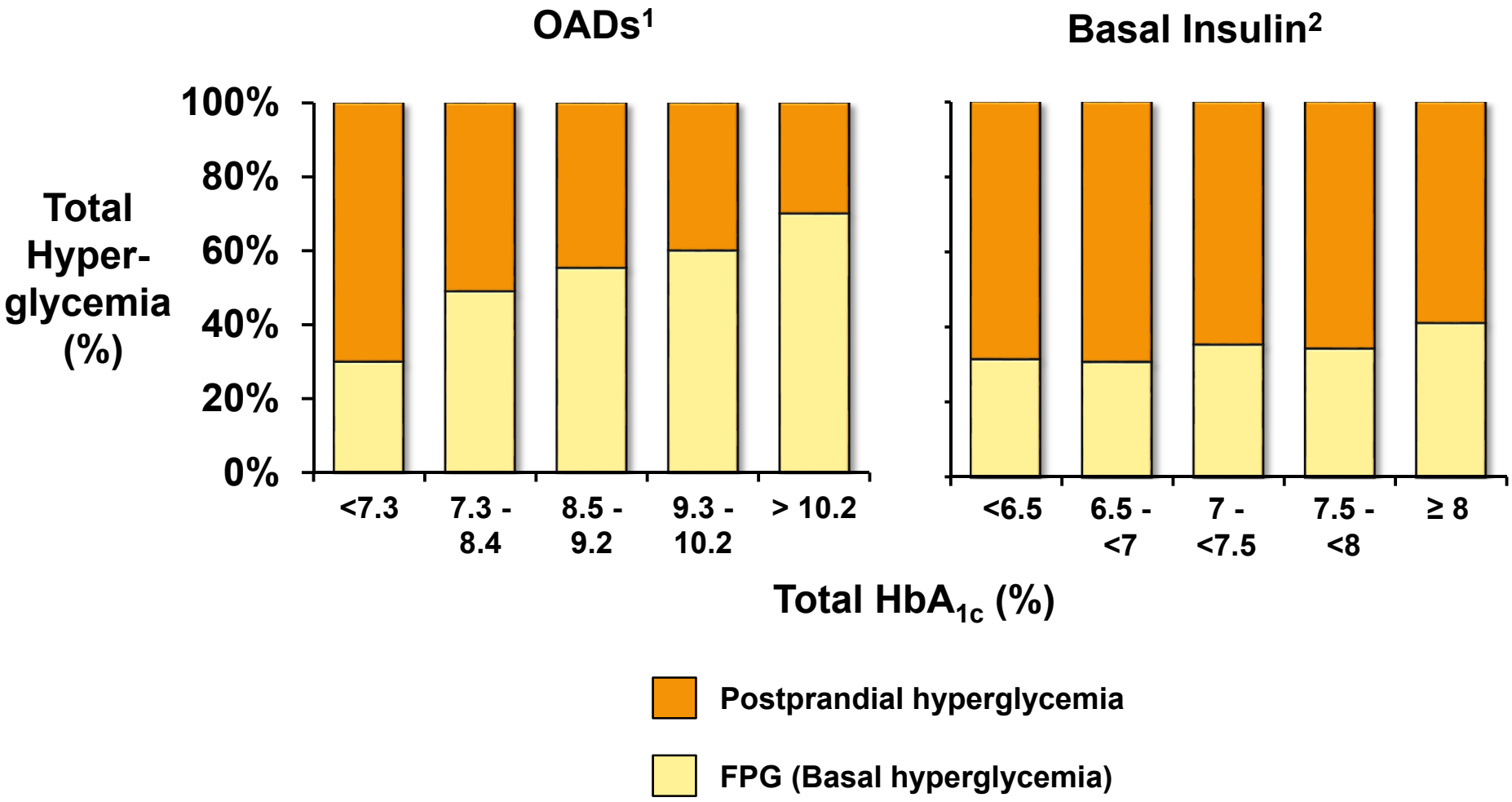
Temple University School of Medicine

Many Patients Unable to Achieve HbA_{1c} Targets



Hoerger (2008)

Need to Control Both FPG and PPG



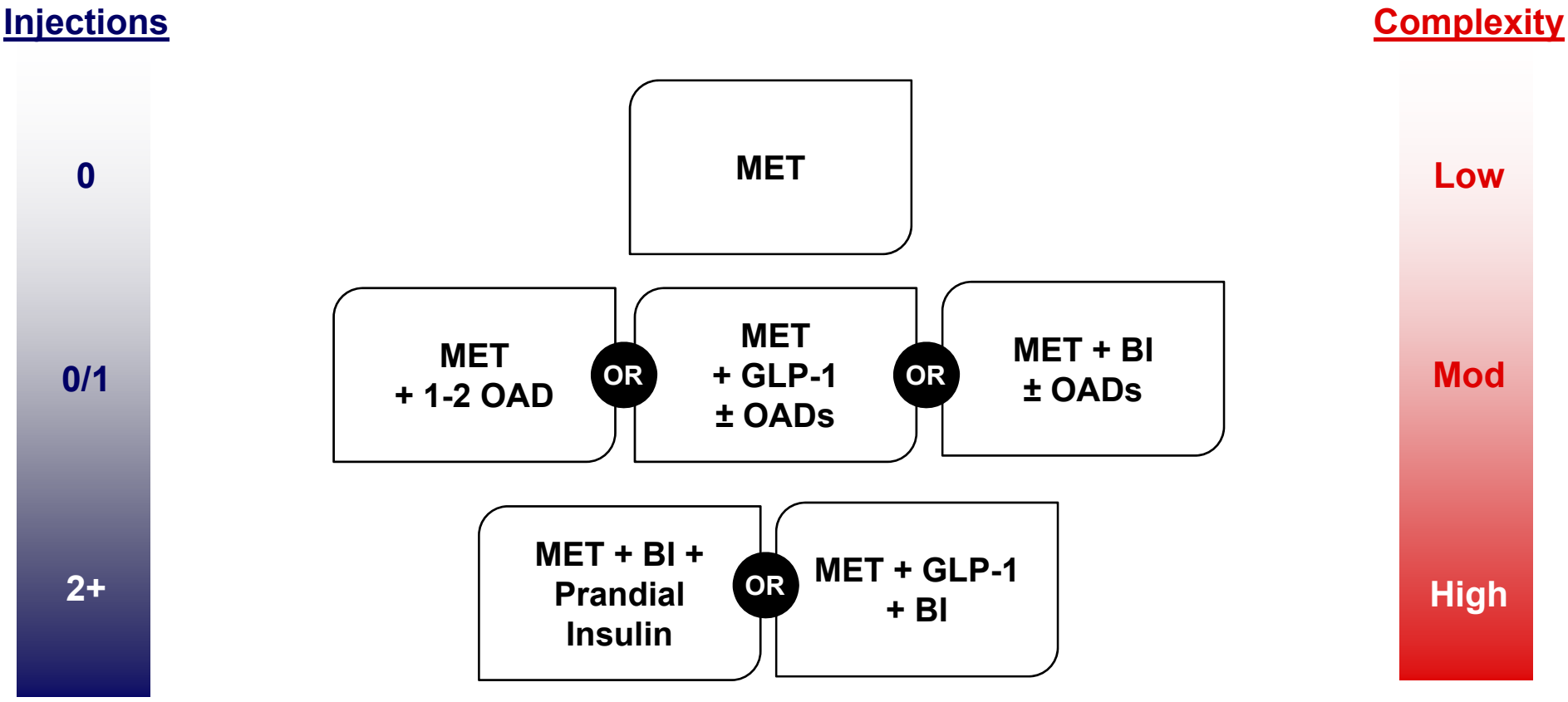
1. Adapted from Monnier (2003); 2. Riddle (2011)

Current Antiglycemic Therapy in Type 2 Diabetes

Metformin +	Efficacy	Hypoglycemic risk	Weight change	Side effects
Sulfonylureas	High	Moderate	Gain	Hypoglycemia
Thiazolidinediones	High	Low	Gain	Edema, heart failure, fracture
DPP-4 Inhibitors	Intermediate	Low	Neutral	Arthralgia
SGLT-2 Inhibitors	Intermediate	Low	Loss	GU, dehydration, ketoacidosis
GLP-1 Agonists	High	Low	Loss	GI
Basal Insulin	Highest	High	Gain	Hypoglycemia
Prandial Insulin	High	High	Gain	Hypoglycemia

GI = Gastrointestinal, GU = Genitourinary
Adapted from American Diabetes Association (ADA) (2016)

Progressive Complexity of Current Treatment Options



BI = Basal Insulin; MET = Metformin

Factors Contributing to Clinical Inertia and Delay in Advancing Therapy

- Treatment complexity
- Fear of additional medicines
- Fear of needles
- Fear of weight gain and hypoglycemia
- Desire not to use multiple injections or check blood sugars throughout day

Unmet Medical Need for Patients Not at Goal on OADs or Basal Insulin

- Achieve better HbA_{1c} by addressing both FPG and PPG
- Combat clinical inertia
  - Simplify patients injectable regimen
  - Mitigate weight gain
  - Minimize side effects
  - Minimize hypoglycemia

Lixisenatide / iGlarLixi Mechanism of Action

John Newton, PhD

Vice President, Pharmacokinetics, Dynamics and Metabolism

Sanofi

Complementary Actions of Lixisenatide and Lantus

Lixisenatide

- ↓ Blood glucose (Glucose dependent)
  - ↓ Gastric emptying
  - ↑ Insulin secretion
  - ↓ Glucagon secretion
- Low risk of hypoglycemia
- ↓ Body weight
- ↓ Post prandial glucose

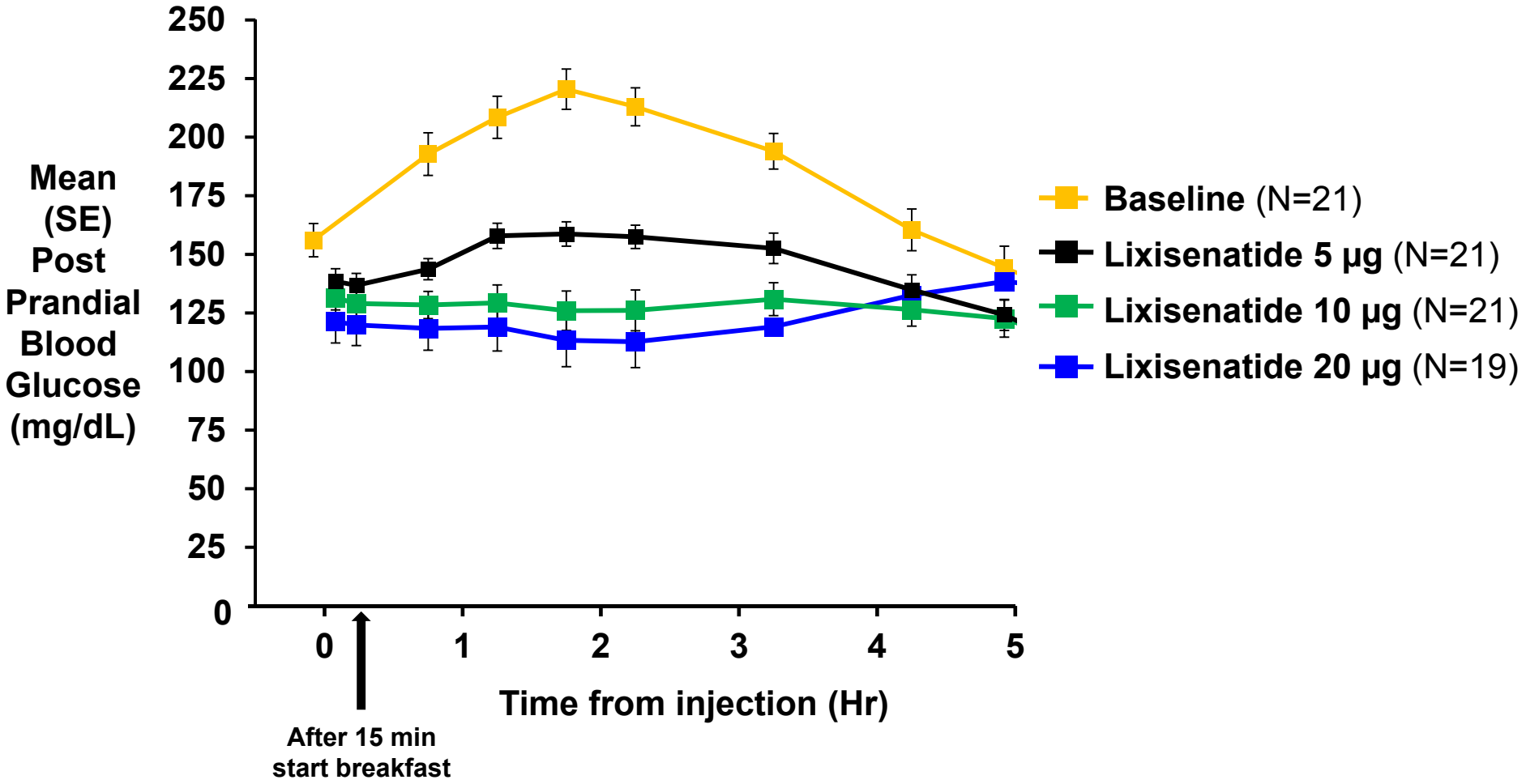
Lantus

- ↓ Blood glucose (Glucose independent)
  - ↑ Uptake by muscle
  - ↑ Uptake ↓ Synthesis by liver
  - ↑ Uptake by adipose tissue
- Risk of hypoglycemia
- ↑ Body weight
- ↓ Fasting glucose

iGlarLixi Represents Novel Approach to Diabetes Treatment

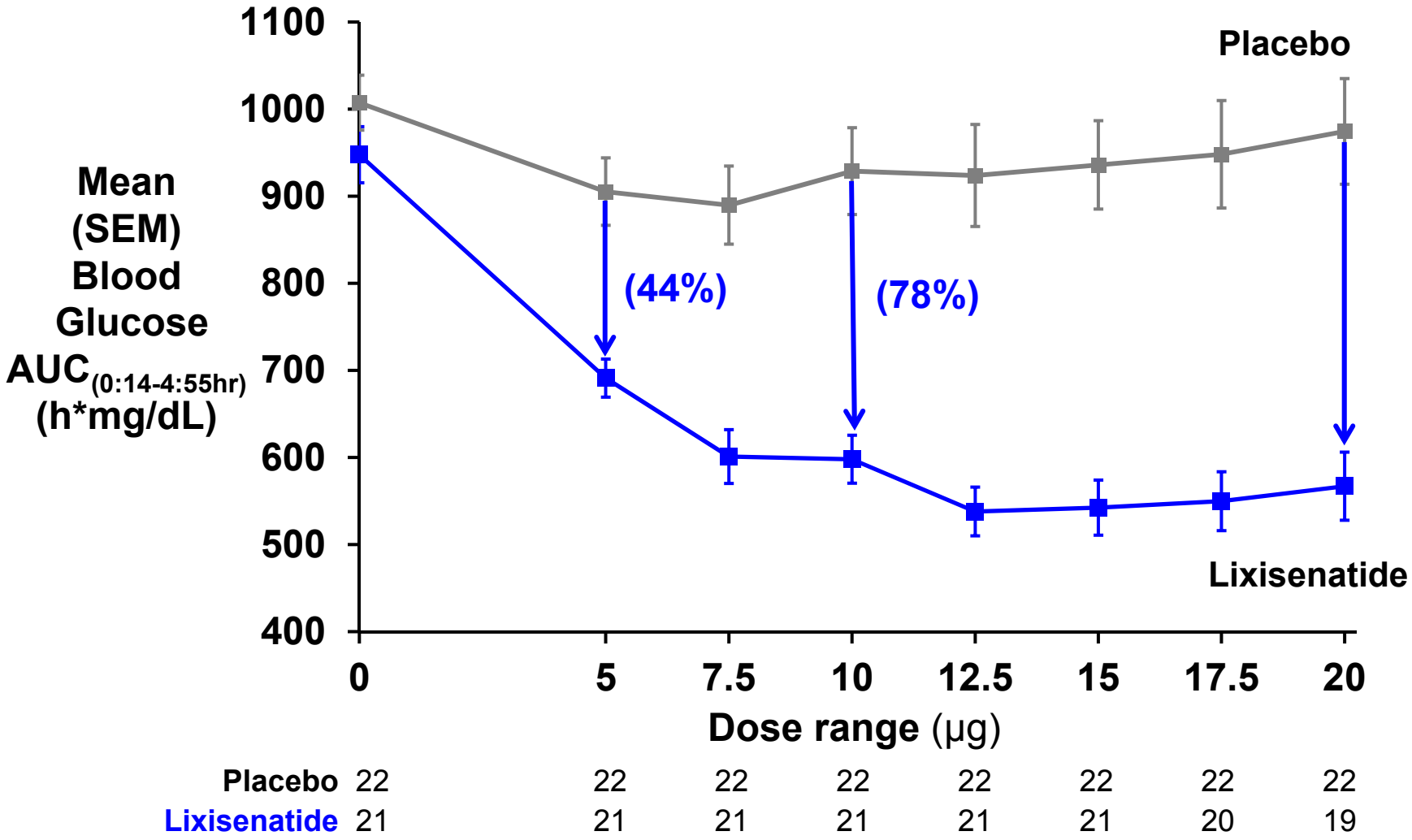
- Simultaneous reduction of FPG and PPG
- Well-established titration approaches for Lantus employed for titration of iGlarLixi
  - Basis for use of Lantus units in dosing of iGlarLixi

Lixisenatide Suppresses PPG Levels



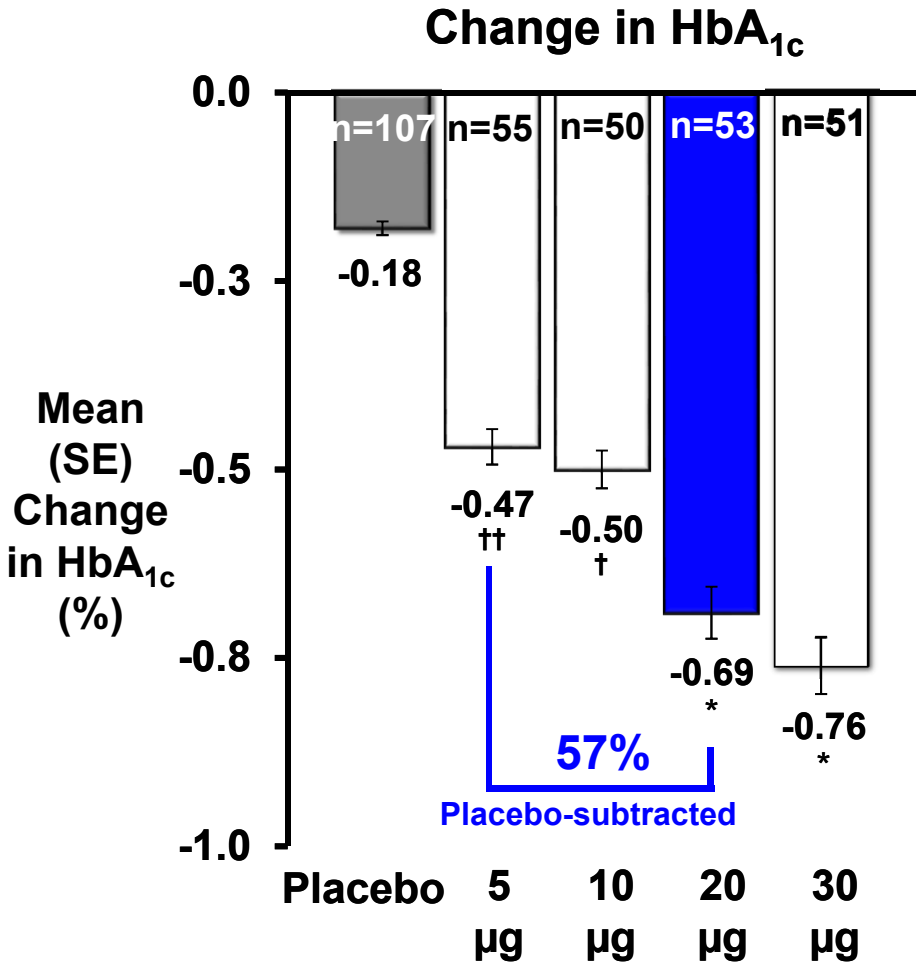
Patients with T2DM, multiple ascending dose study, ACT6011

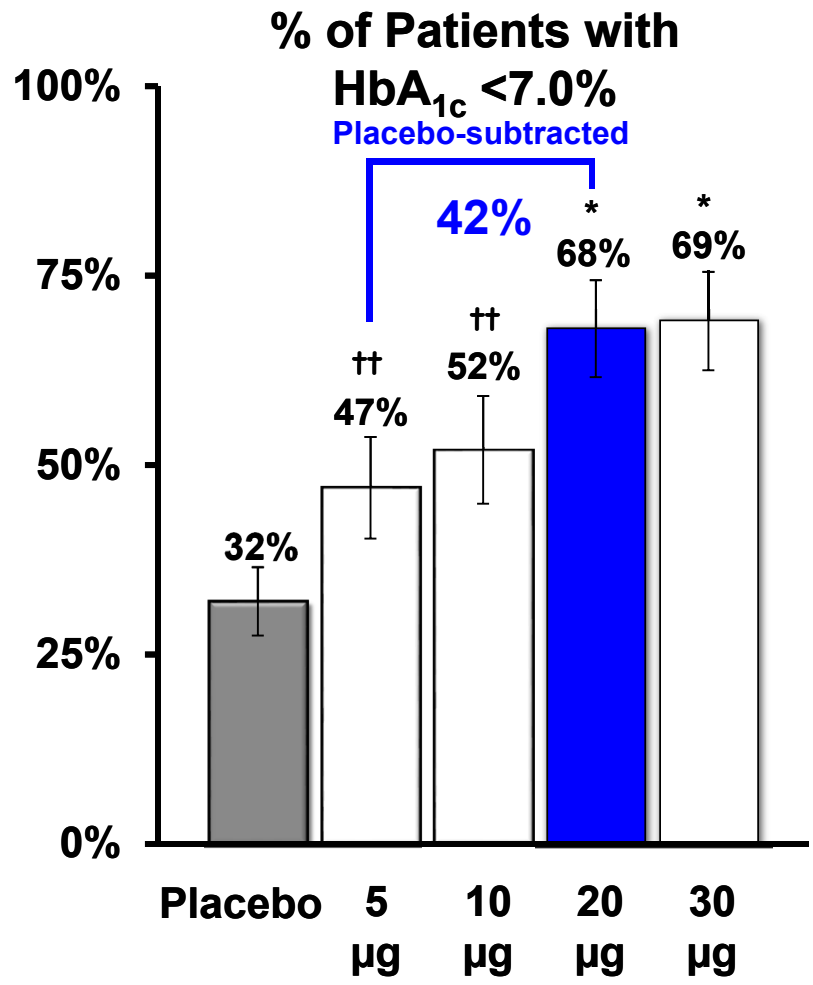
Lixisenatide Reduces PPG Over Dose Range of 5 – 20 µg / T2DM



Patients with T2DM, ascending dose range for 4 weeks, ACT6011

Lixisenatide Produces Maximal Efficacy by 20 µg Once Daily





*p<0.0001, †p<0.005, ††p<0.05 vs. placebo

Patients with T2DM, dose ranging study for 13 weeks, DRI6012

Lixisenatide Active Over Entire 5 – 20 µg Dose Range in iGlarLixi

- Daily doses as low as 5 µg provided clinically meaningful improvement
  - PPG, HbA_{1c} and responder rates
- Doses >20 µg did not further improve PPG or overall efficacy
  - Lower tolerability

Clinical Considerations for iGlarLixi Fixed Ratio Combination (FRC)

- Lantus low dose of 10U for initiation in insulin naïve patients
- Lantus high dose covering majority of patients' needs
- Lixisenatide low dose of 5 µg
- Lixisenatide high dose of 20 µg
- Initiate basal insulin users on iGlarLixi with limited reduction in insulin dose

iGlarLixi Provides Benefits to Wide Range of Patients – Pen A (2:1 Ratio)

10U Lantus / 5 µg Lixi **40U Lantus / 20 µg Lixi**

- Ratio based on
  - Low Lantus dose of 10U
  - Low Lixisenatide dose of 5 µg
- High Lantus dose of 40U based on highest Lixisenatide dose of 20 µg

iGlarLixi Provides Benefits to Wide Range of Patients – Pen B (3:1 Ratio)

30U Lantus / 10 µg Lixi **60U Lantus / 20 µg Lixi**

- Ratio based on
  - High Lantus dose of 60U
  - High Lixisenatide dose of 20 µg
- Low Lantus dose of 30U based on highest initiation Lixisenatide dose of 10 µg

iGlarLixi – Two Components with Distinct and Complementary Actions

- Lixisenatide
  - Lowers blood glucose by glucose dependent mechanisms – low risk of hypoglycemia
  - Reduces weight
  - Significant impact on PPG
  - Effective dose range: 5-20 µg
- Lantus
  - Lowers blood glucose by glucose independent mechanisms – risk of hypoglycemia
  - Leads to weight gain
  - Significant impact on FPG

Lixisenatide and iGlarLixi Efficacy

Rachele Berria, MD, PhD

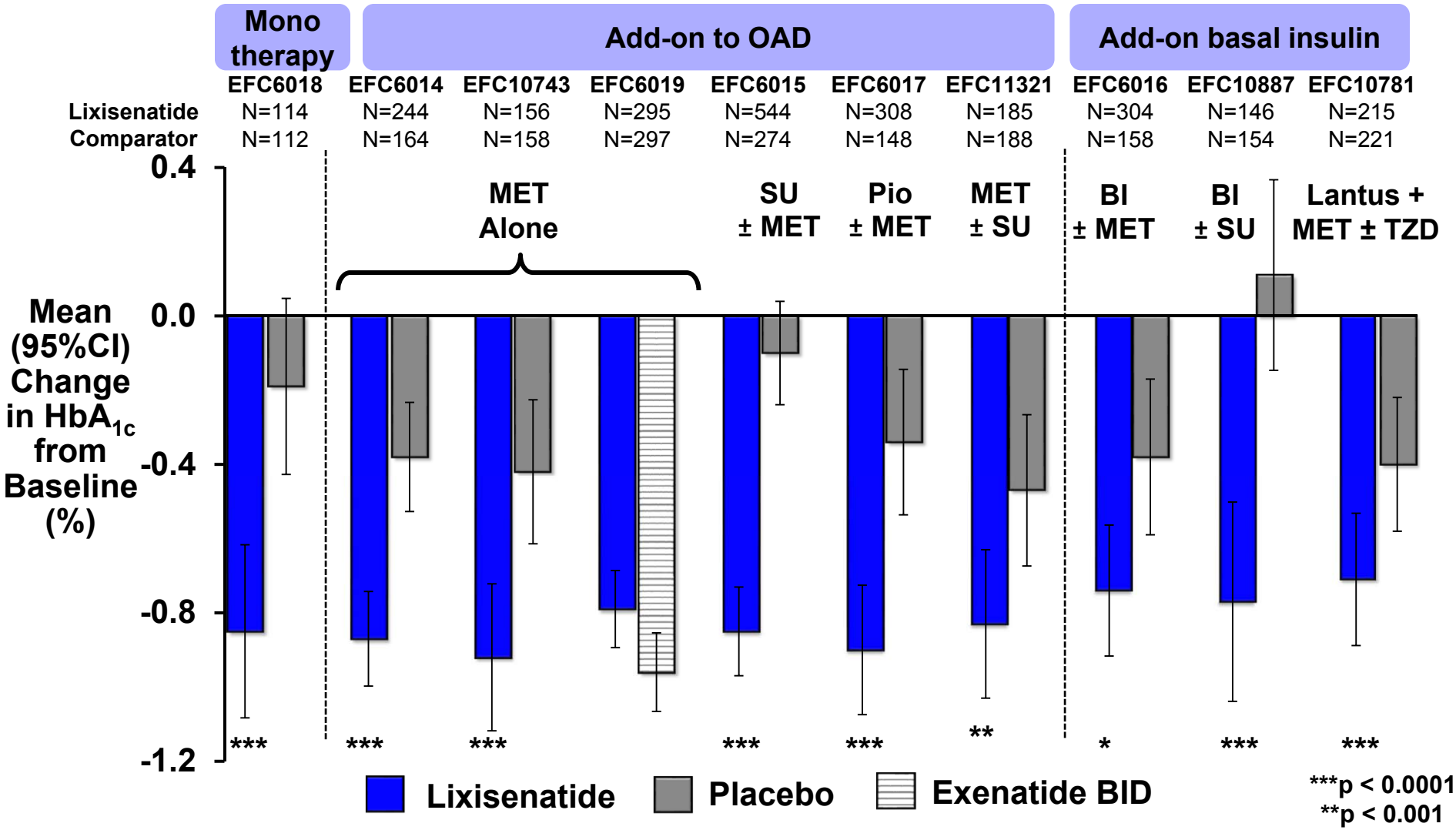
Vice President and Head of Diabetes Medical Unit

Sanofi

Lixisenatide and iGlarLixi Development Programs

- Lixisenatide Phase 2/3 studies
  - N=13,433 patients
  - ~60% treated for ≥ 1 year
- iGlarLixi Phase 3 studies
  - Study 404: patients uncontrolled on oral antidiabetic medications
  - Study 405: patients on basal insulin requiring intensification

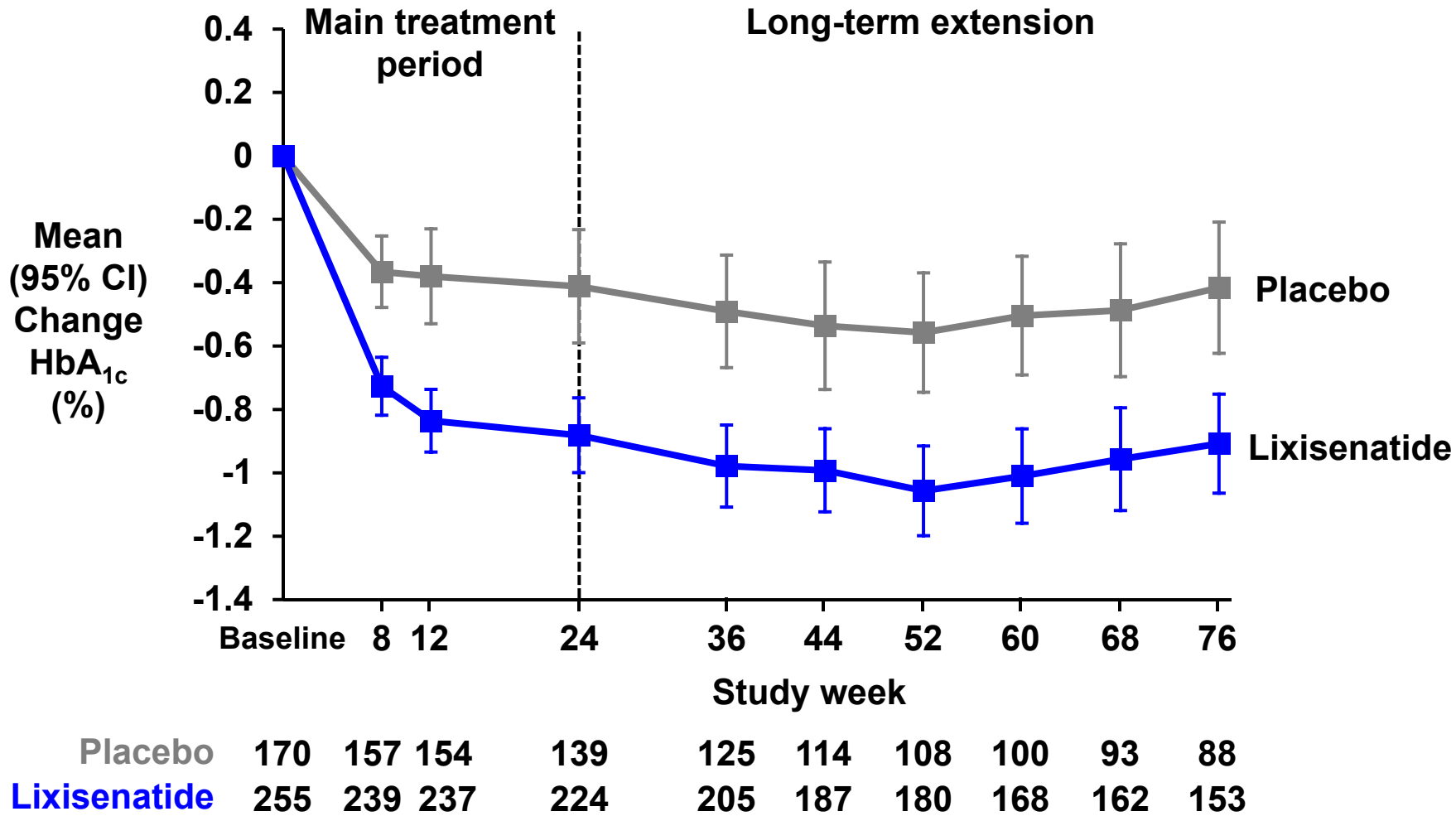
Lixisenatide Produces Consistent and Clinically Relevant Reduction in HbA_{1c}



***p < 0.0001
**p < 0.001
*p=0.0002

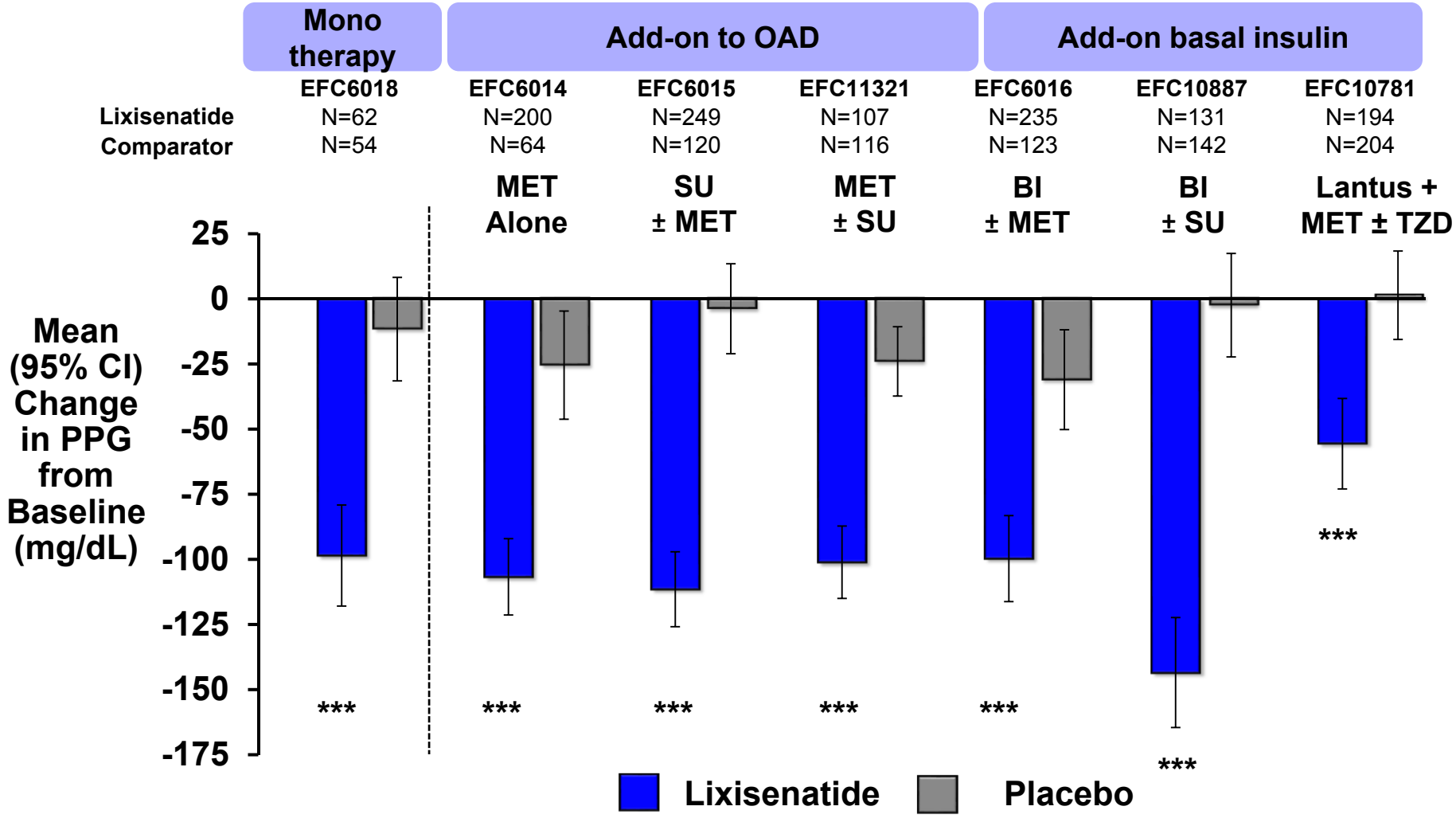
mITT population, 24-week data (12-week for monotherapy), LOCF

Glucose Lowering Efficacy Maintained Over 76 Weeks



Add-on to MET EFC6014

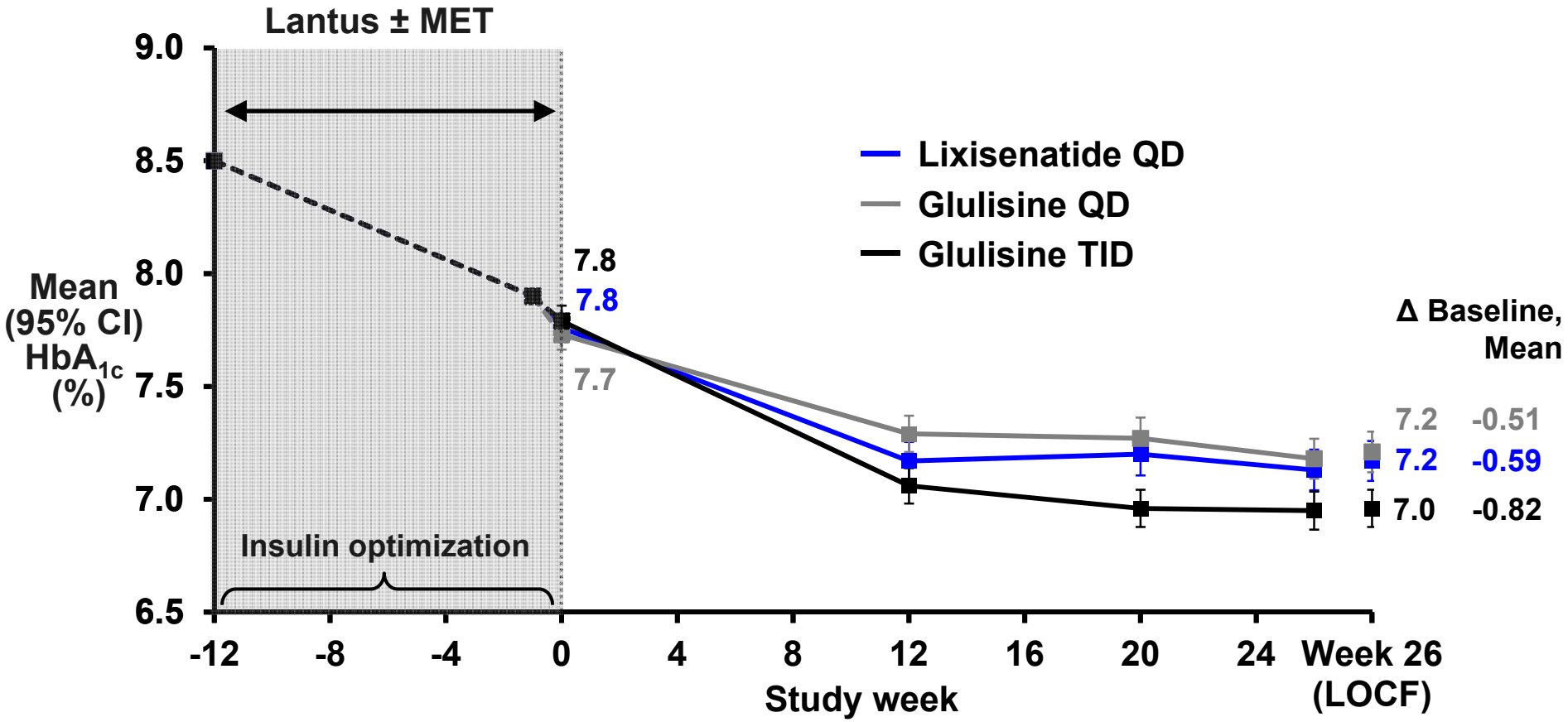
Lixisenatide Demonstrated Beneficial Effects on 2-Hour PPG



mITT population, 24-week data (12-week for monotherapy)

***p< 0.001

Once Daily Lixisenatide Non-Inferior to Prandial Insulin for HbA_{1c} Reduction

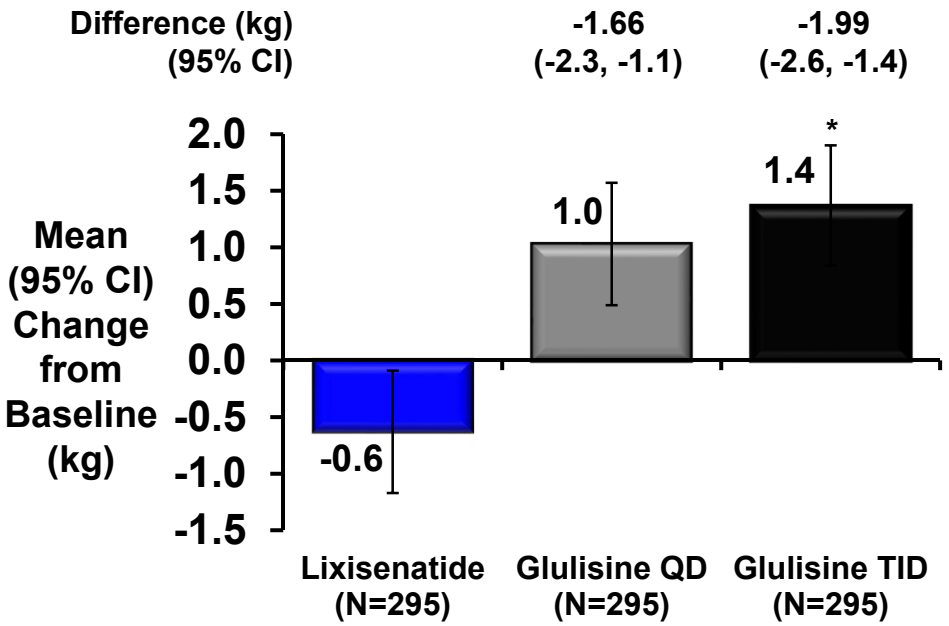


Lixisenatide	297	284	280	263	292
Glulisine QD	298	289	282	275	292
Glulisine TID	295	288	287	283	295

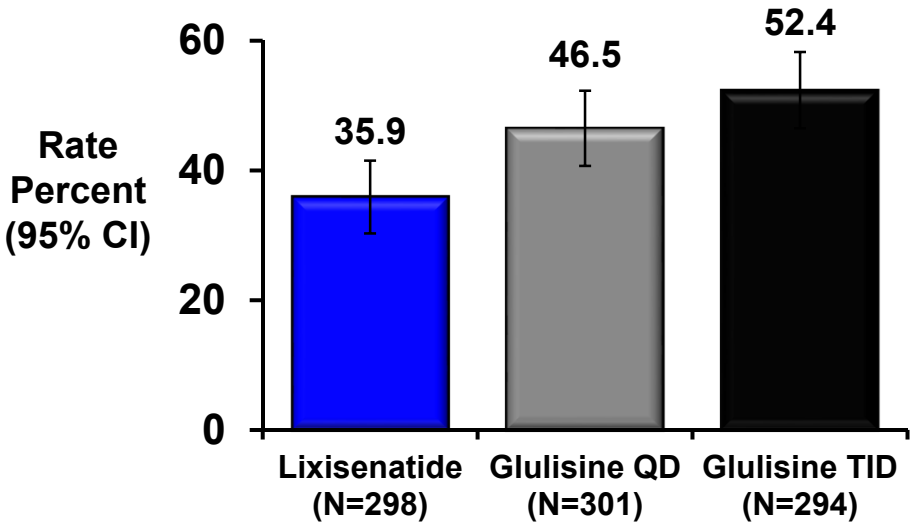
Study EFC12626
mITT for randomized populations

Once Daily Lixisenatide Demonstrated Clinical Advantage Compared to Prandial Insulin

Body Weight[1]



Hypoglycemia[2]

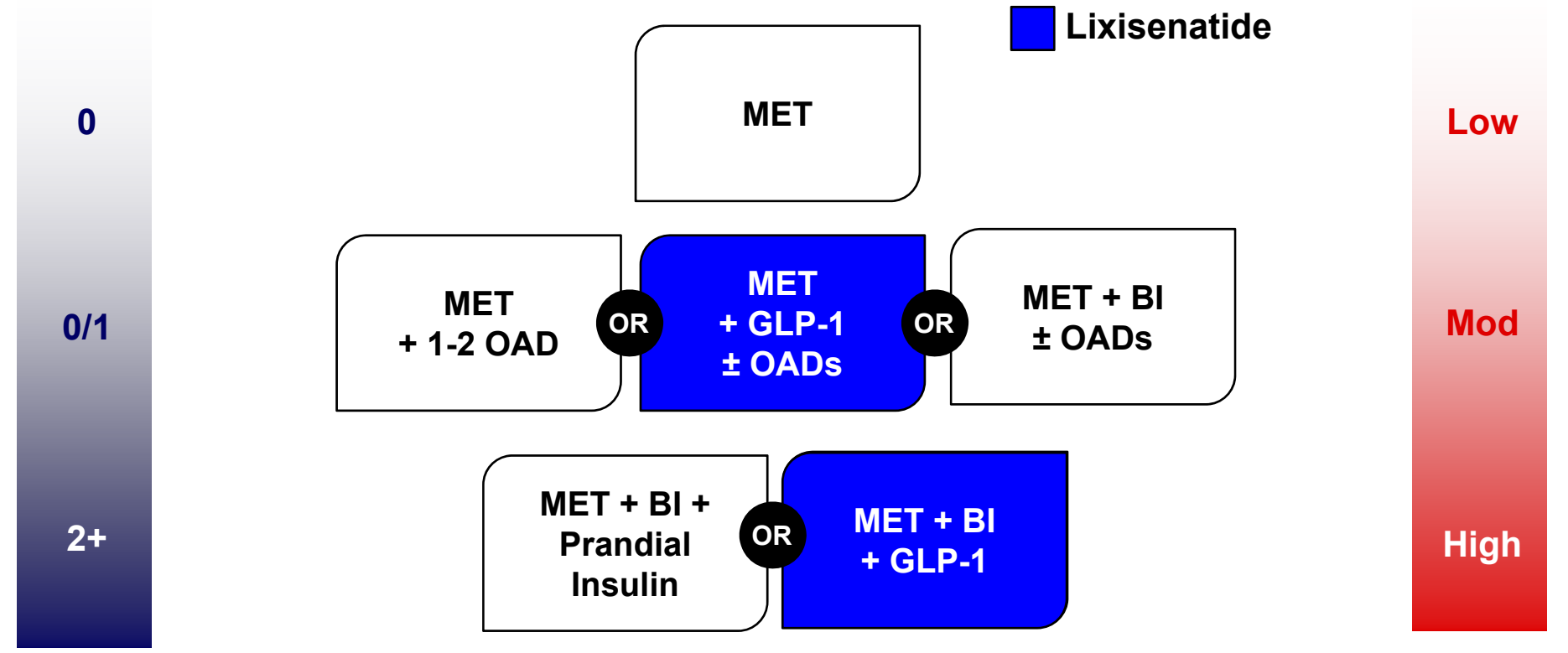


Study EFC12626

1. mITT population
2. Symptomatic hypoglycemia (as reported by Investigator) Safety Population

*p<0.0001

Diabetes Treatment Algorithm



BI = Basal insulin; MET = Metformin
Adapted and modified from ADA

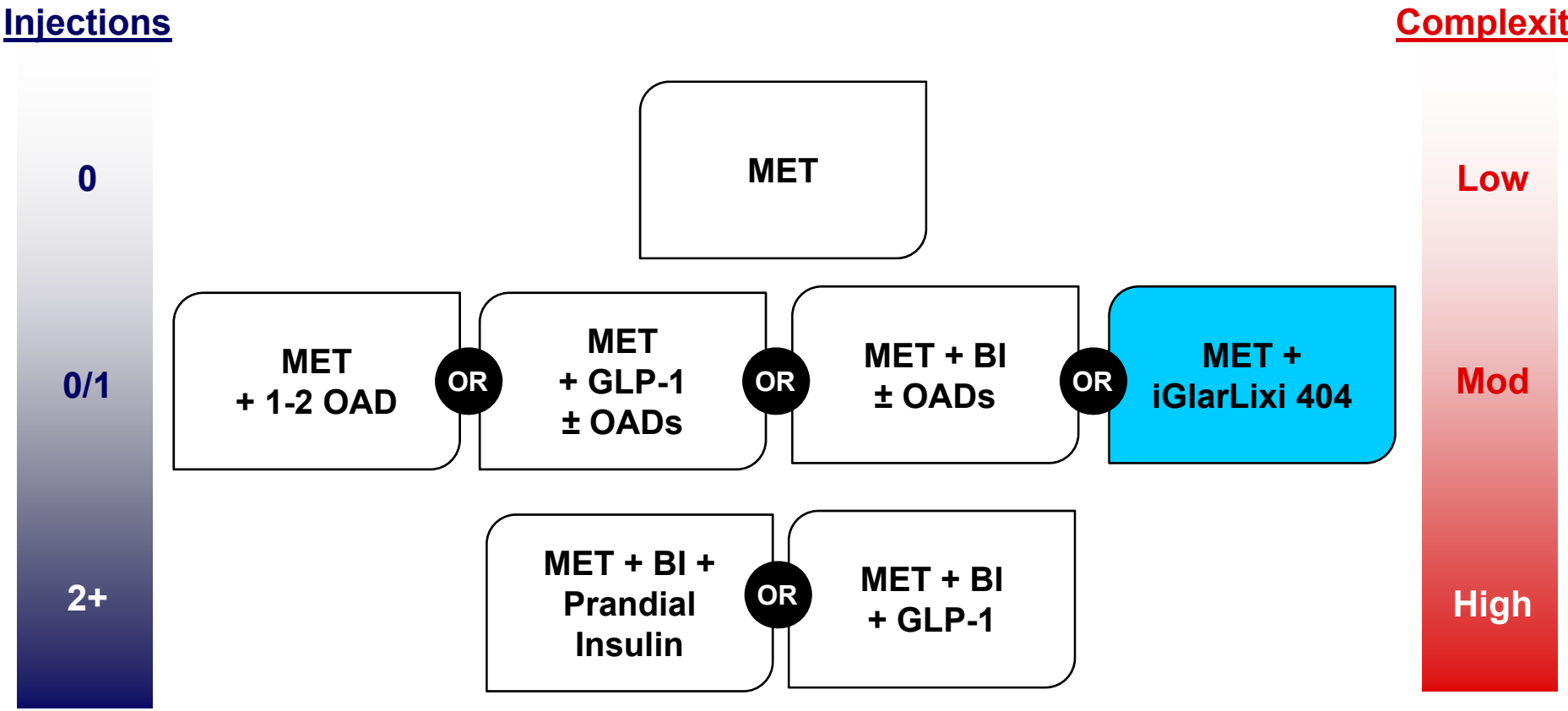
iGlarLixi Efficacy

Statistical Methods – Phase 3 Studies

	iGlarLixi Program
Primary endpoint*	Change from baseline in HbA_{1c} at Week 30
Primary methods	MMRM – including all data regardless of treatment discontinuation or rescue
Missing HbA_{1c}	<6% and similar between groups
Sensitivity analyses	Several methods following recommendations from 2010 NRC report on missing data

***Based on mITT population**
MMRM: Mixed-effect model with repeated measures
NRC: National Research Council

iGlarLixi: Alternative to Intensification with Basal Insulin or GLP-1 Agonist



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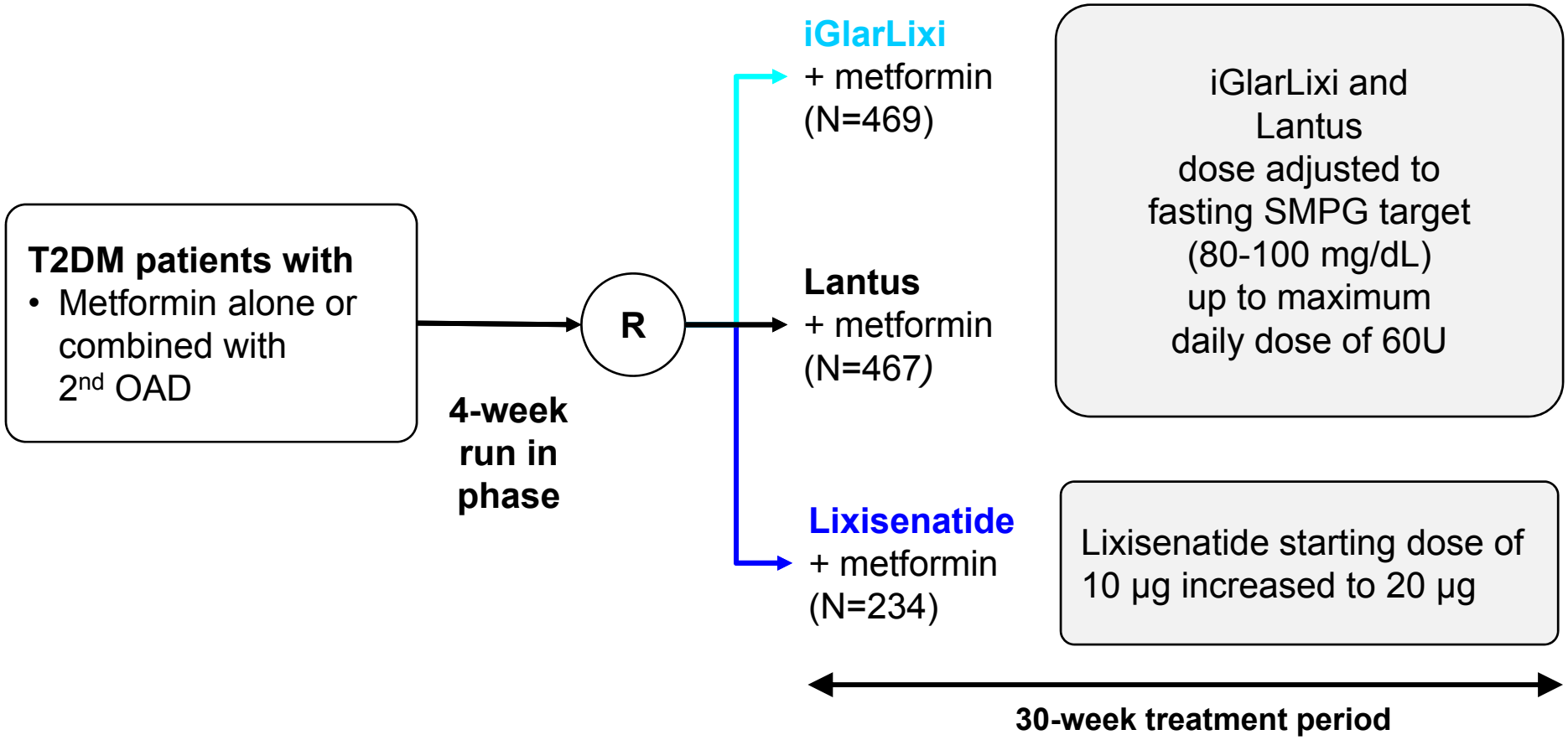
Adapted and modified from ADA

Study 404: Patients Uncontrolled on OADs, 3-Arm Study



- Primary endpoint: change in HbA_{1c}, at Week 30

Study 404: Baseline Demographics Well-Balanced

	Study 404 (N=1170)		
	iGlarLixi (N=469)	Lantus (N=467)	Lixisenatide (N=234)
Gender - Male	47%	51%	57%
Race			
Caucasian	89%	90%	92%
Black	7%	7%	5%
Other	4%	3%	3%
Age (mean, yrs)	58	58	59
BMI (mean/baseline)	32	32	32
BMI ≥ 30	63%	62%	68%

Randomized population

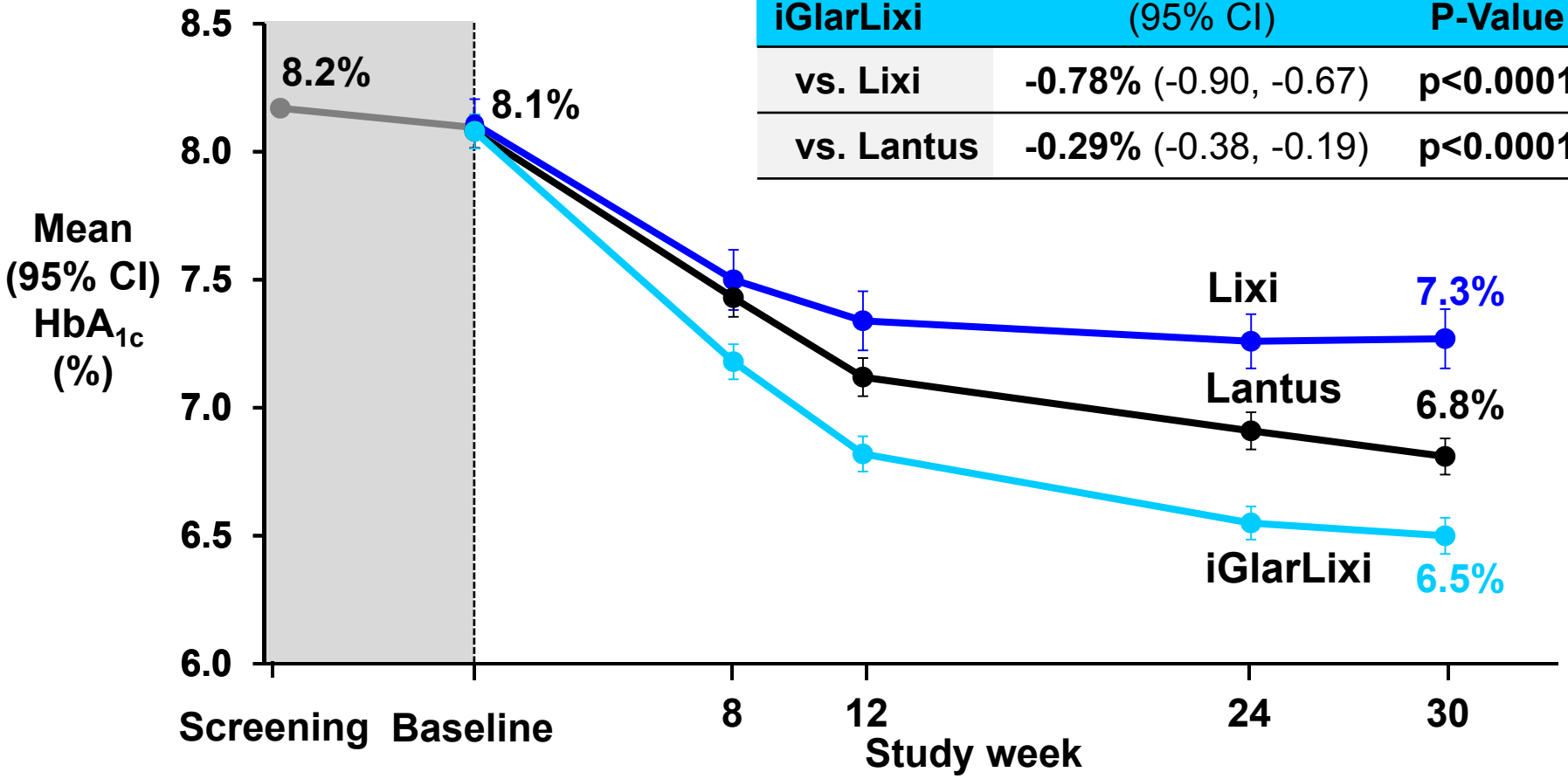
Study 404: Baseline Disease Characteristics Well-Balanced

Screening	Study 404 (N=1170)		
	iGlarLixi (N=469)	Lantus (N=467)	Lixisenatide (N=234)
Duration of diabetes (mean, yrs)	8.9	8.7	8.9
HbA_{1c} at screening (mean)	8.2%	8.2%	8.3%
HbA_{1c} at baseline (mean)	8.1%	8.1%	8.1%
Use of 2 OADs (patients)	58%	58%	57%
Duration of use (mean, yrs)	4.0	4.6	3.9

Randomized population

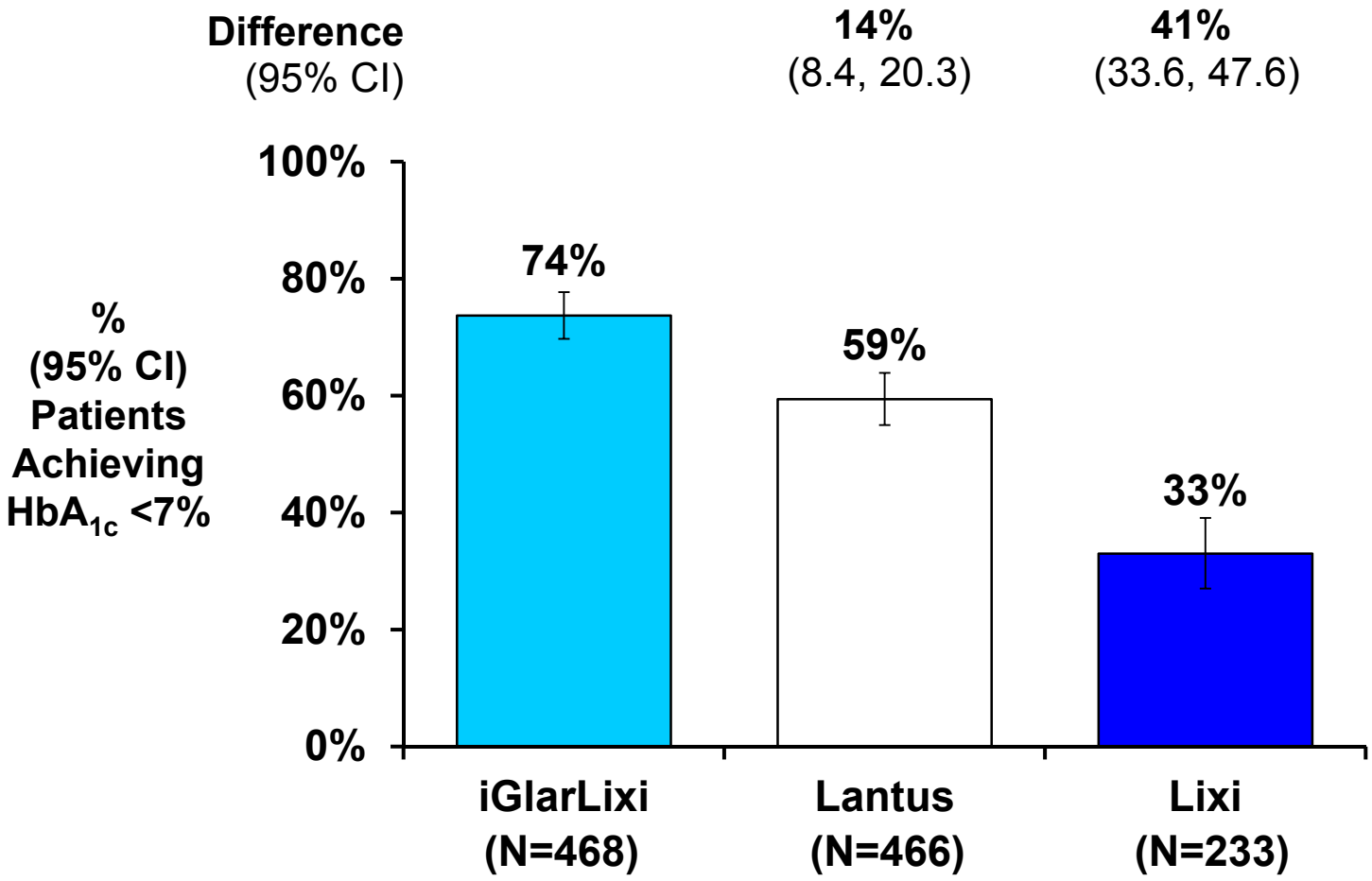
Study 404 Primary Endpoint: iGlarLixi Demonstrated Superior HbA_{1c} Reduction

iGlarLixi	Mean Difference (95% CI)	P-Value
vs. Lixi	**-0.78%** (-0.90, -0.67)	**p<0.0001**
vs. Lantus	**-0.29%** (-0.38, -0.19)	**p<0.0001**



Lixisenatide	232	233	224	224	221	221
Lantus	466	466	456	455	447	446
iGlarLixi	468	468	461	455	447	443

Study 404: More iGlarLixi Patients Achieved Target HbA_{1c} of <7%

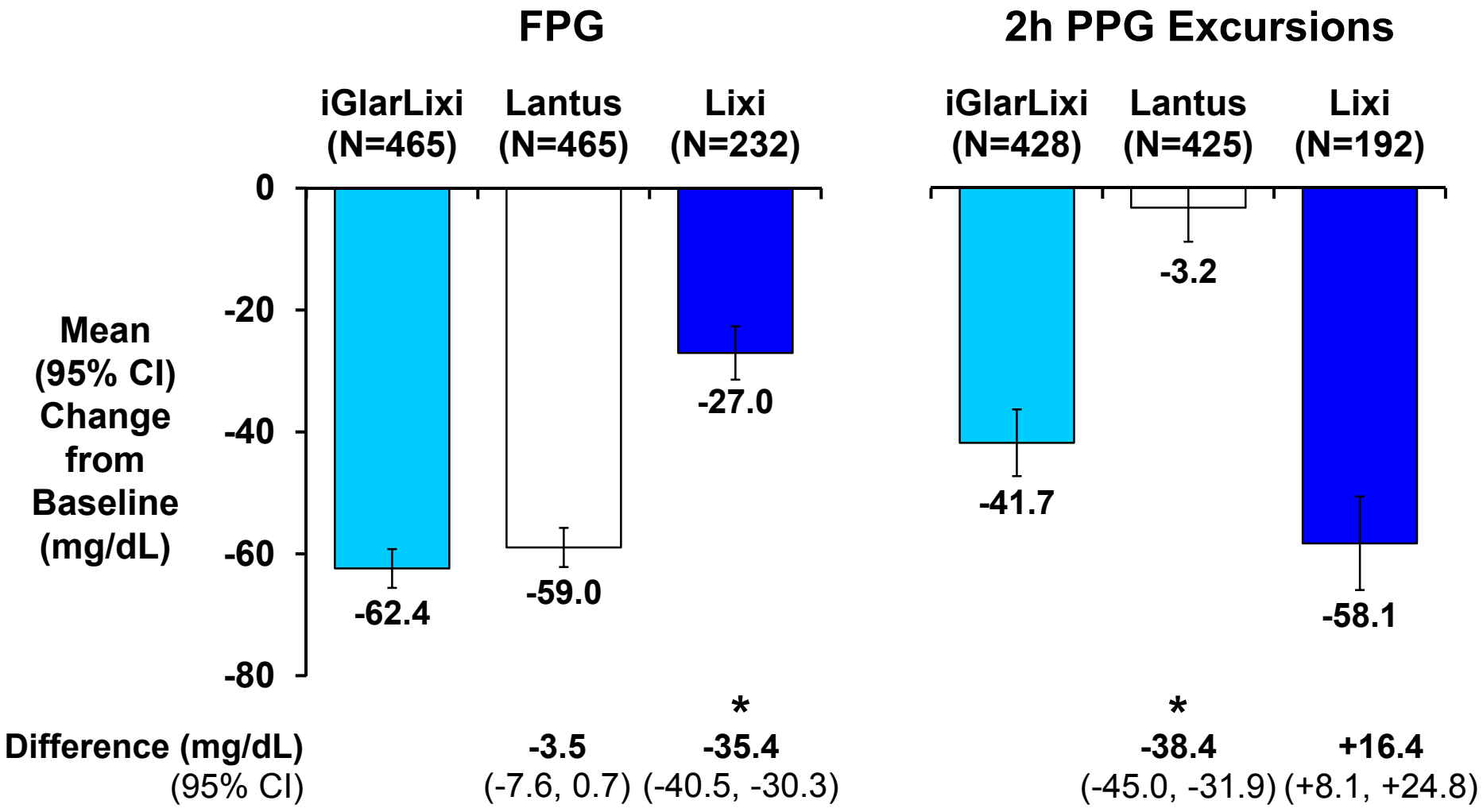


mITT population

Key Secondary Endpoints

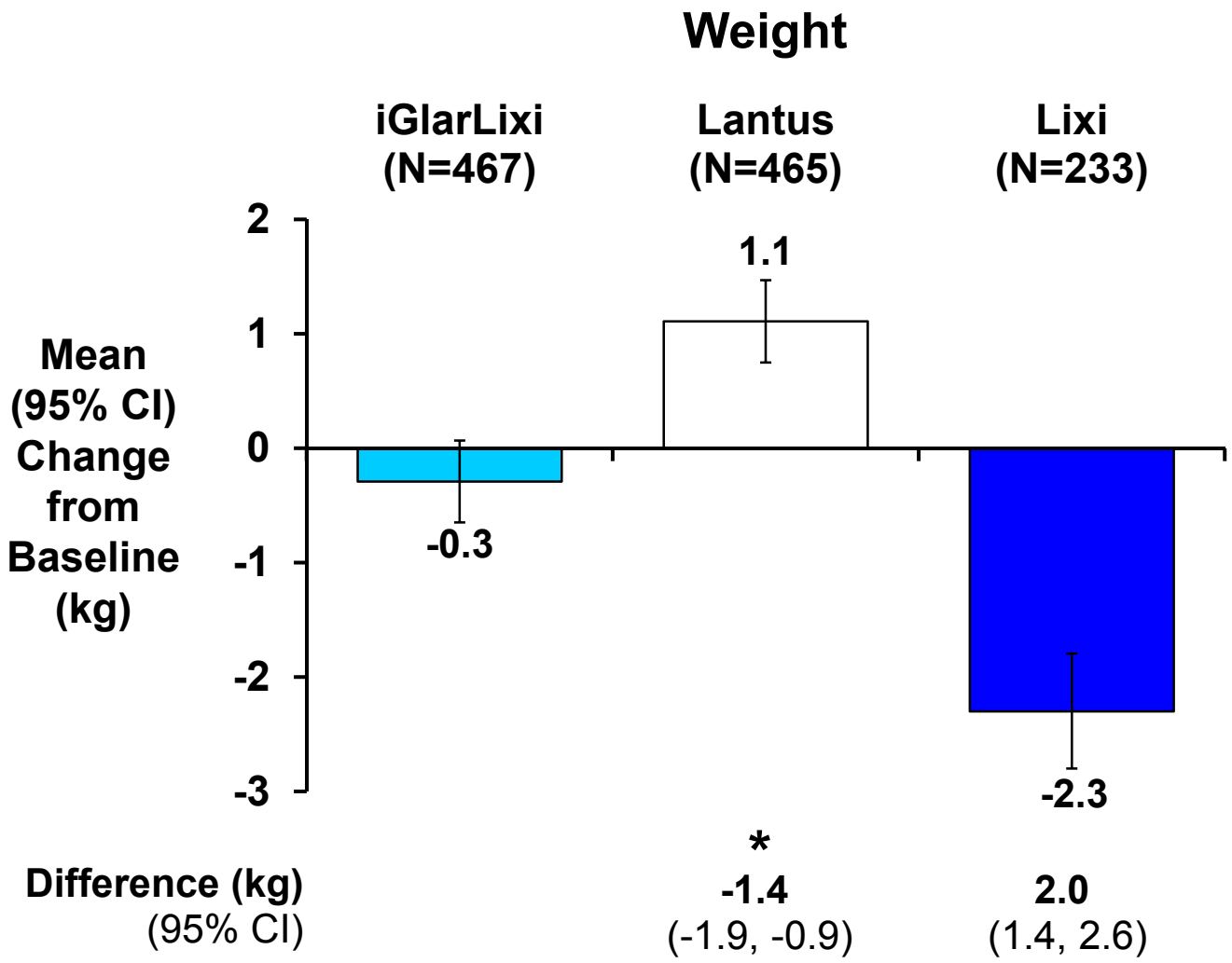
Study 404

Study 404: Lantus Affects FPG, Lixisenatide Affects PPG Excursions



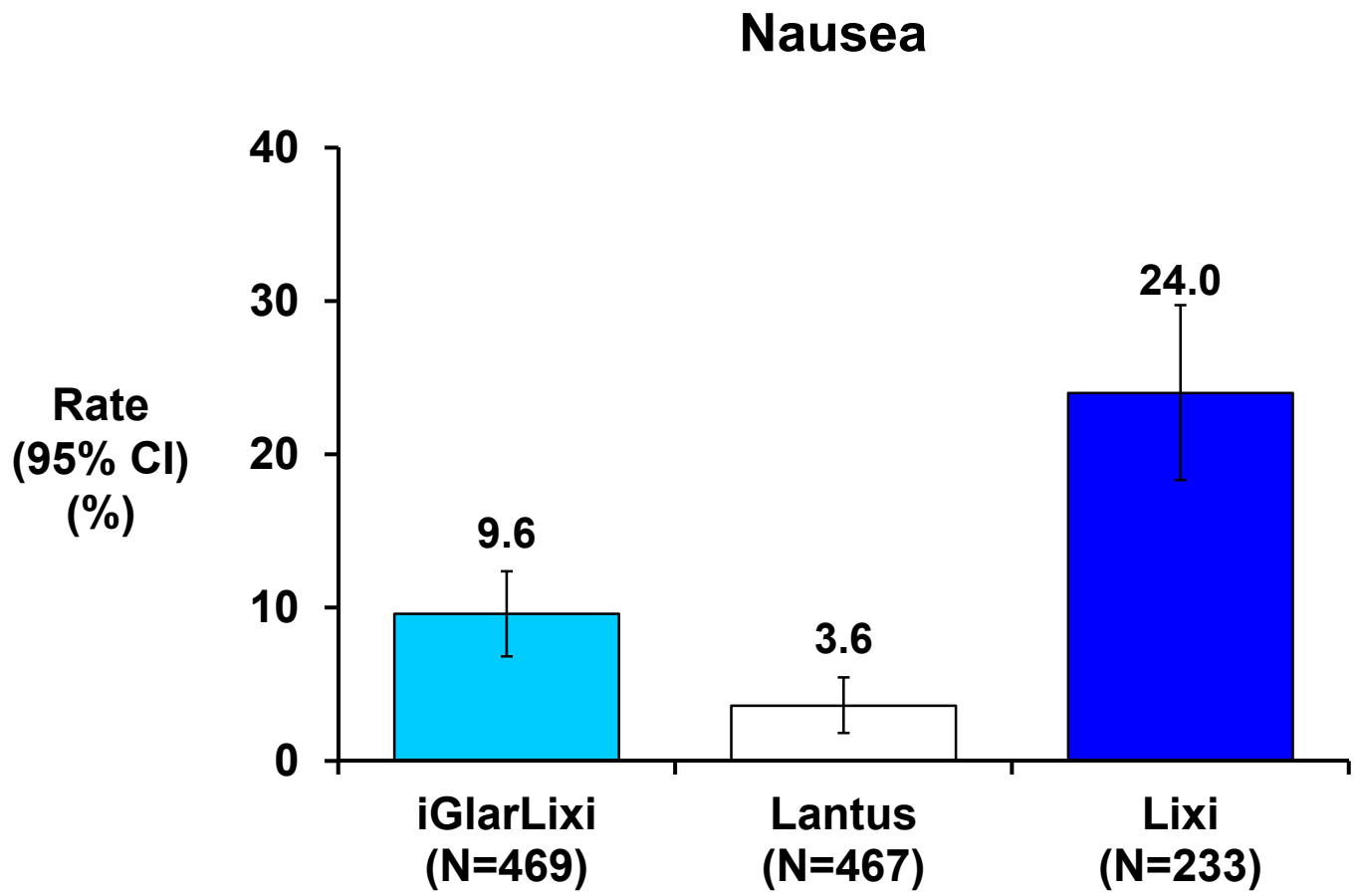
* p<0.0001

Study 404: Lixisenatide in iGlarLixi Mitigates Weight Gain with Lantus



* p<0.0001

Study 404: Lower Rate of Nausea with iGlarLixi than Lixisenatide

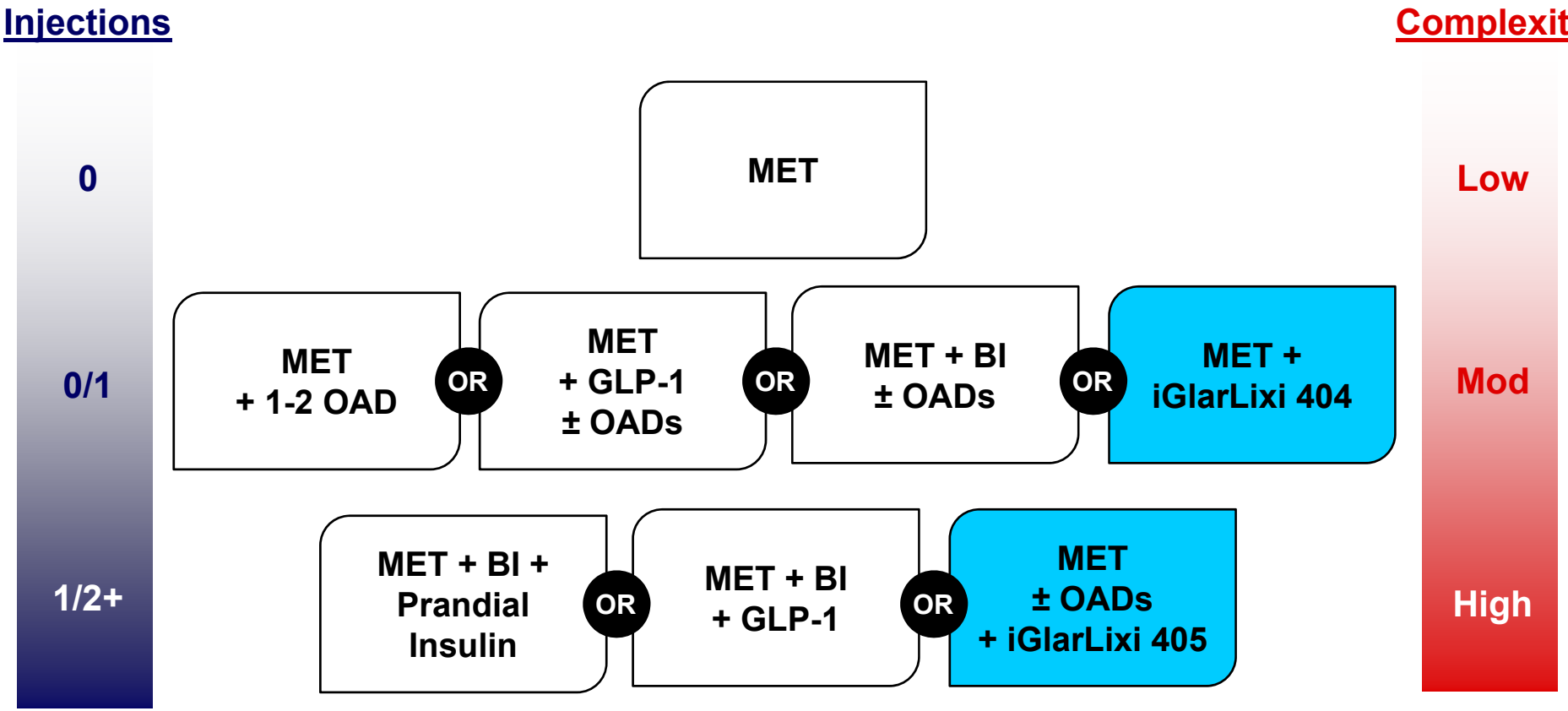


Safety Population

Patients on Basal Insulin Needing Intensification

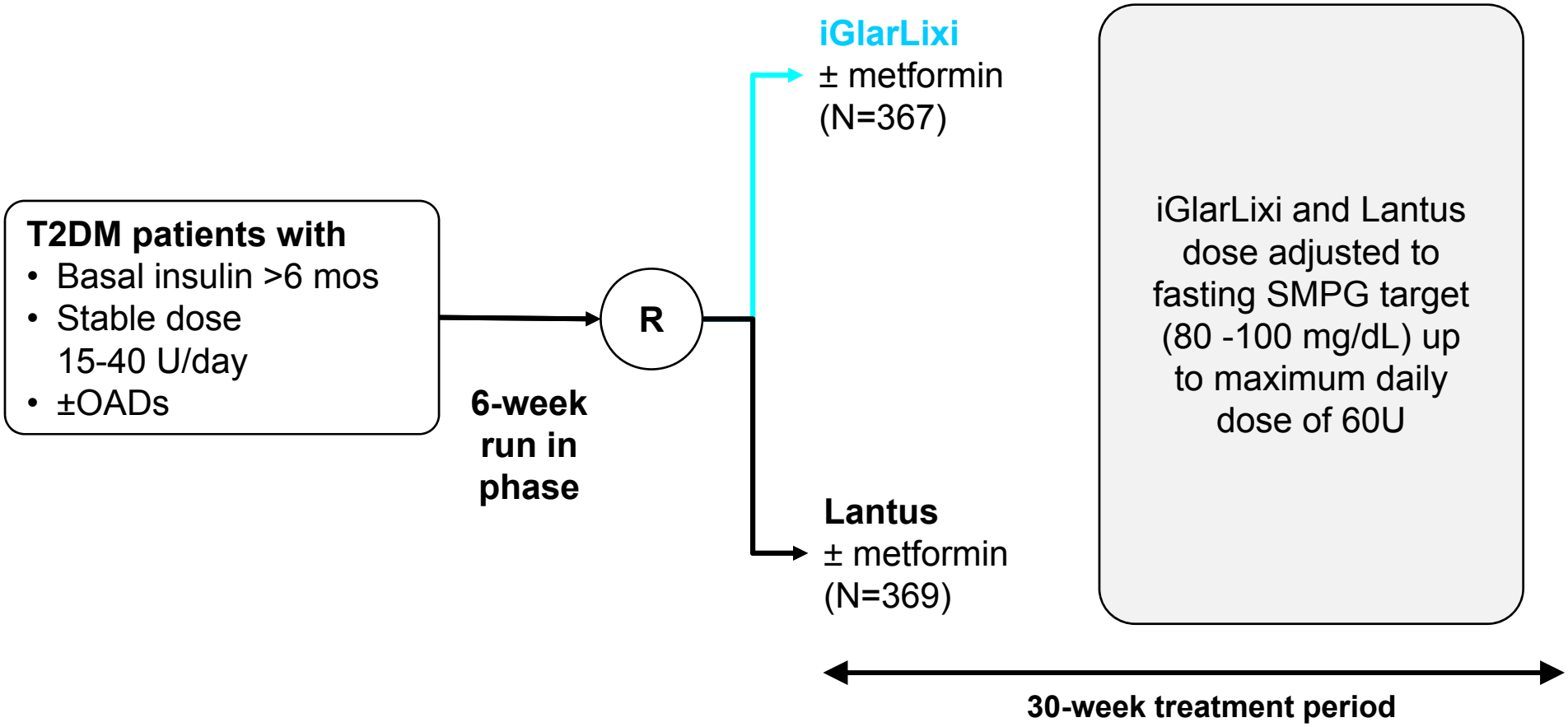
Study 405

iGlarLixi: Alternative to Intensification with Mealtime Insulin or GLP-1



BI = Basal Insulin; MET = Metformin
Adapted and modified from ADA

Study 405: Comparison to Lantus



- Primary endpoint: change in HbA_{1c} at Week 30

Study 405: Baseline Demographics Well-Balanced

	Study 405 (N=736)	
	iGlarLixi (N=367)	Lantus (N=369)
Gender – Male	**45%**	**49%**
Race		
Caucasian	**92%**	**92%**
Black	**5%**	**6%**
Other	**3%**	**2%**
Age (mean, yrs)	**60**	**60**
BMI (mean, baseline)	**31**	**31**
BMI ≥ 30	**58%**	**57%**

Randomized population

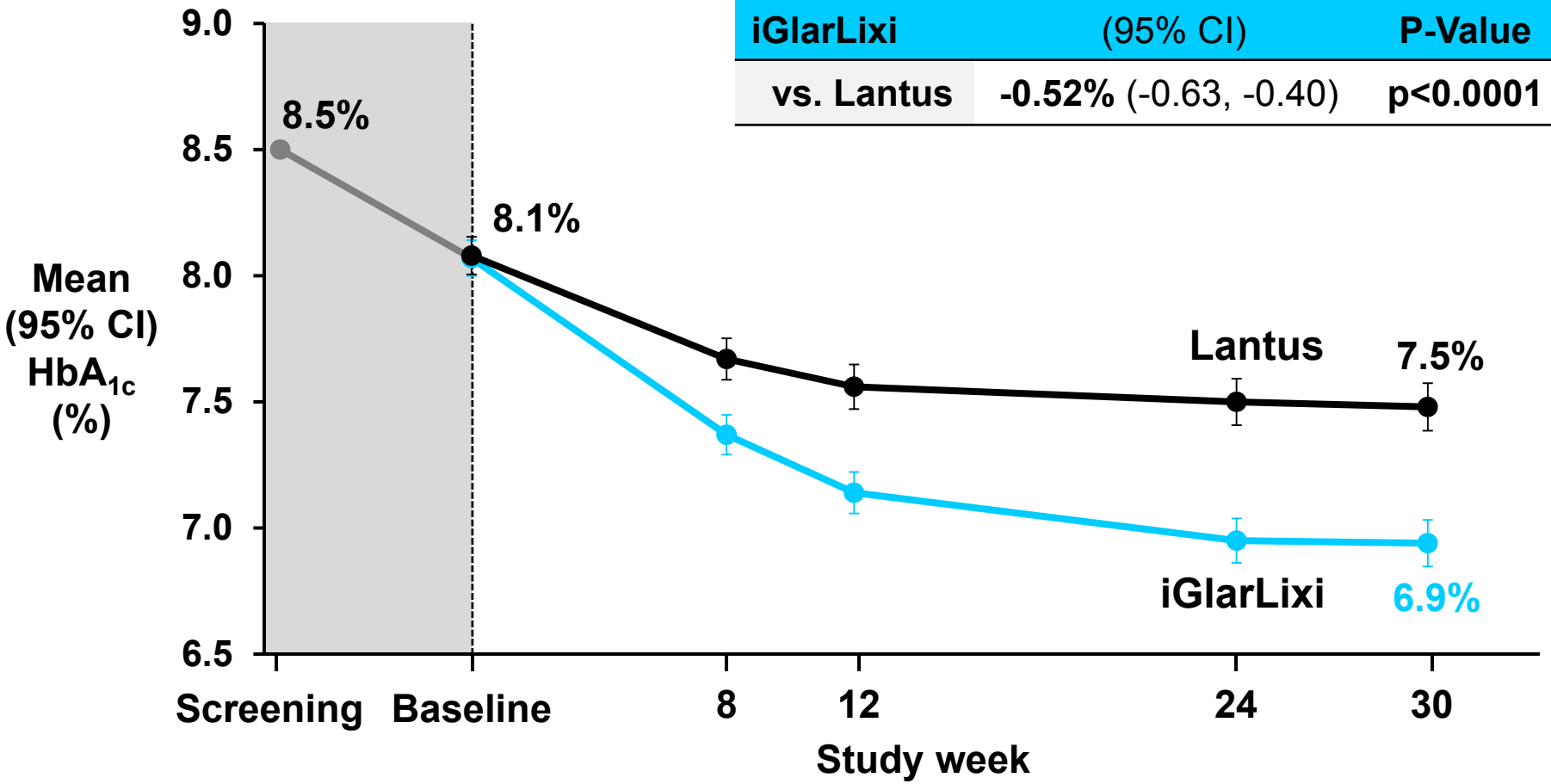
Study 405: Baseline Disease Characteristics Well-Balanced

Screening	Study 405 (N=736)	
	iGlarLixi (N=367)	Lantus (N=369)
Duration of diabetes (mean, yrs)	12.0	12.1
HbA_{1c} at screening (mean)	8.5%	8.5%
HbA_{1c} at baseline (mean)	8.1%	8.1%
Use of 2 OADs (patients)	44%	38%
Duration of use (mean, yrs)	4.4	4.8
Duration of insulin use (mean, yrs)	3.1	3.3

Randomized population

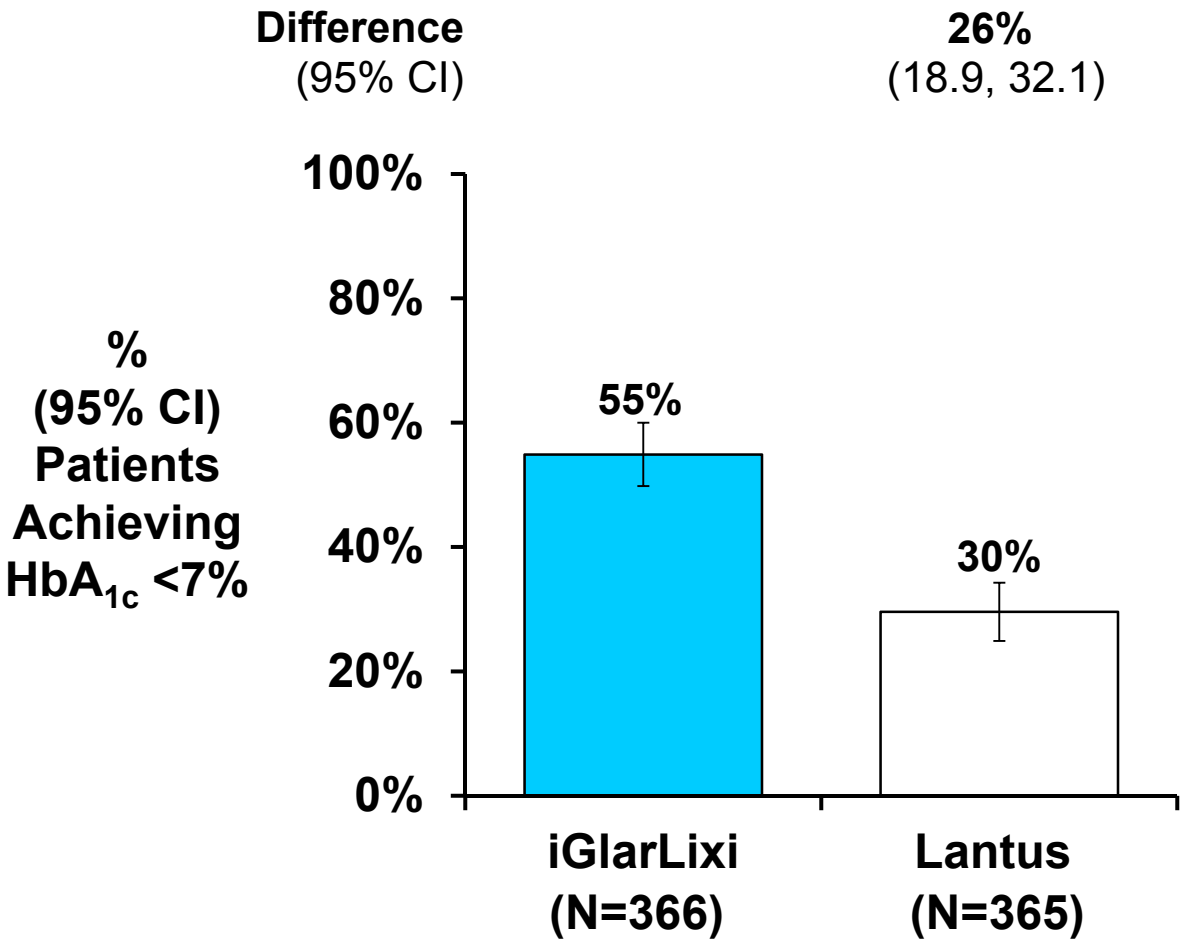
Study 405 Primary Endpoint: iGlarLixi Demonstrated Superior HbA_{1c} Reduction

iGlarLixi	Mean Difference (95% CI)	P-Value
vs. Lantus	**-0.52%** (-0.63, -0.40)	**p<0.0001**



Lantus	365	365	356	360	354	355
iGlarLixi	366	366	357	357	348	346

Study 405: More iGlarLixi Patients Achieved Target HbA_{1c} of <7%

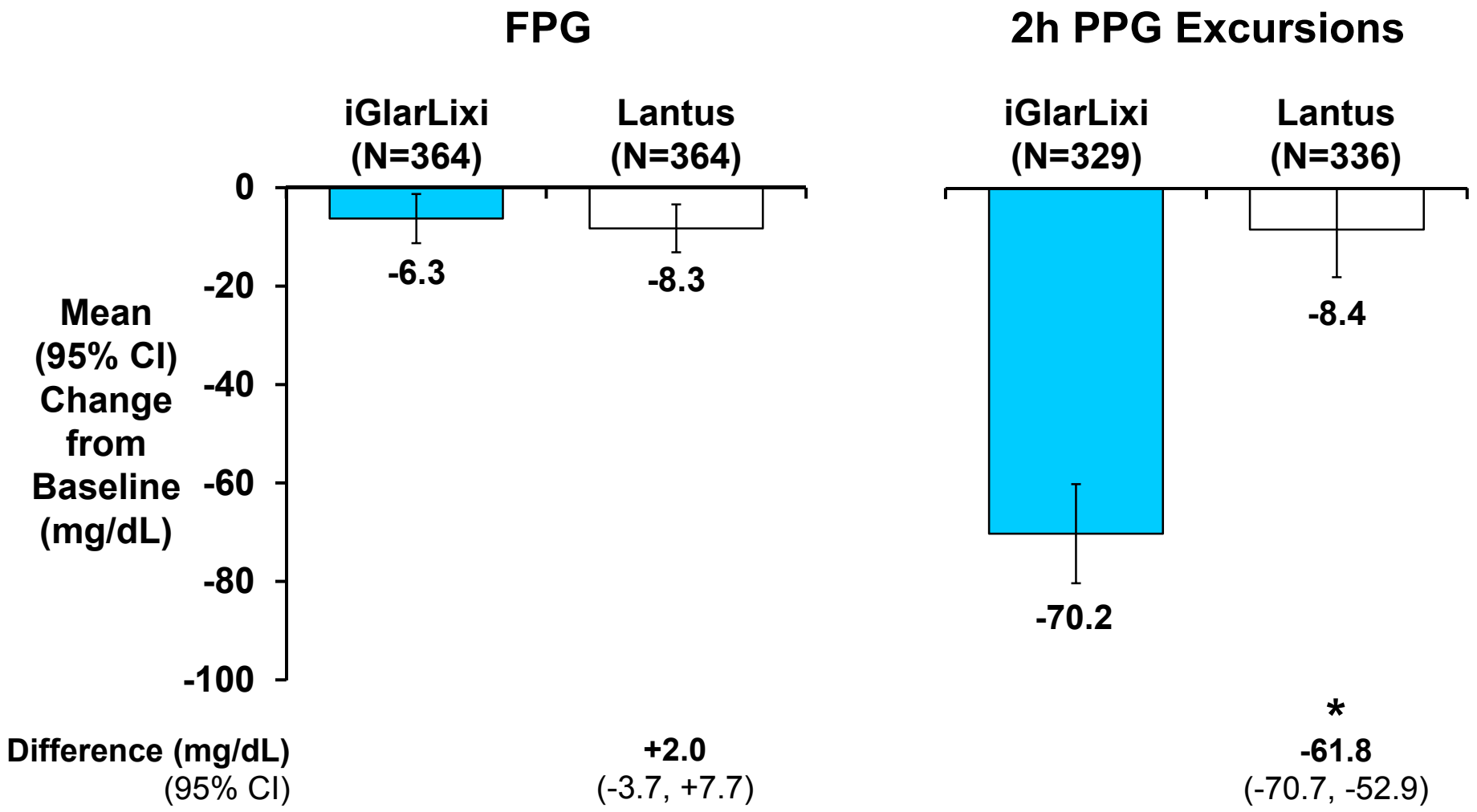


mITT population

Key Secondary Endpoints

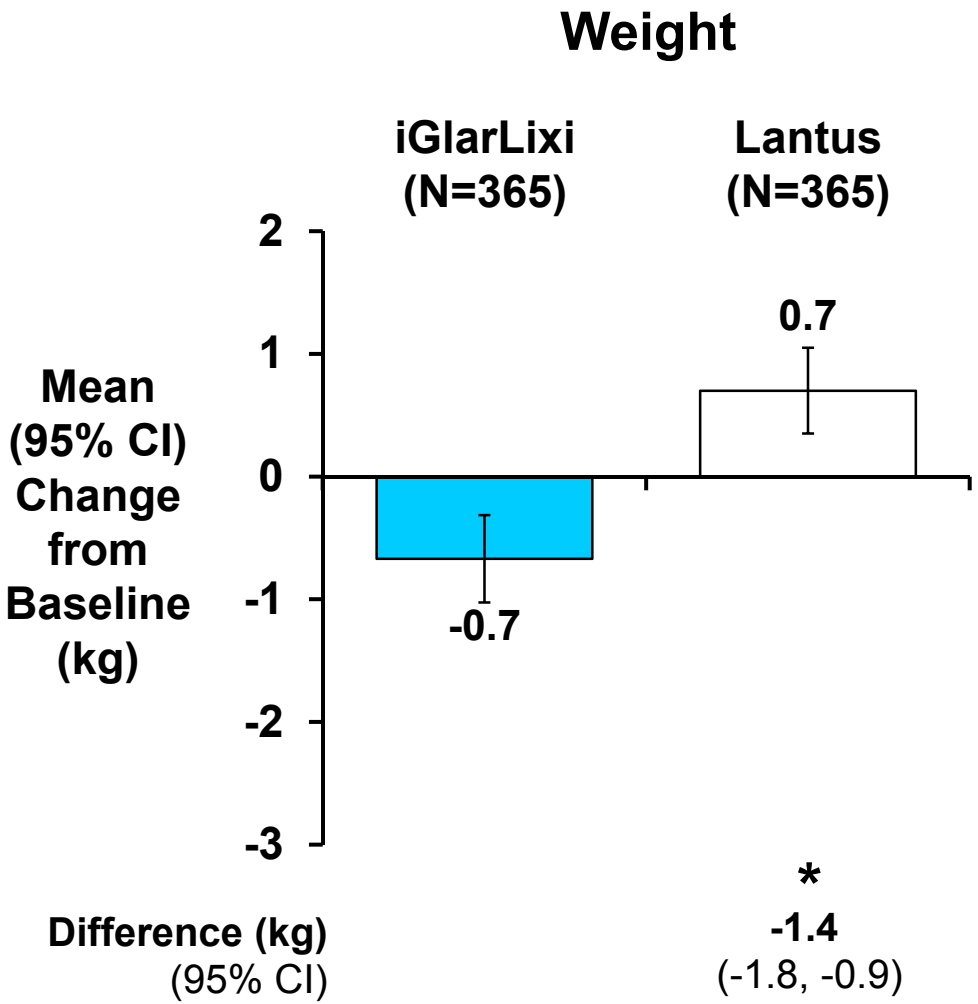
Study 405

Study 405: Lantus Affects FPG, Lixisenatide Affects PPG Excursions



*p<0.0001

Study 405: Lixisenatide in iGlarLixi Mitigates Weight Gain with Lantus



*p<0.0001

iGlarLixi Efficacy Summary

- Superior HbA_{1c} reduction
  - Compared to Lixisenatide and Lantus (Study 404)
  - Compared to Lantus (Study 405)
- Greater number of patients achieving treatment success with iGlarLixi
- Body weight loss / mitigation of body weight gain
- Lower rate of GI events compared with Lixisenatide
- Contribution of both components meets FDA requirement

Lixisenatide / iGlarLixi Safety

Kristen Sharma, MD

Vice President, Global Diabetes and Cardiovascular Pharmacovigilance Unit

Sanofi

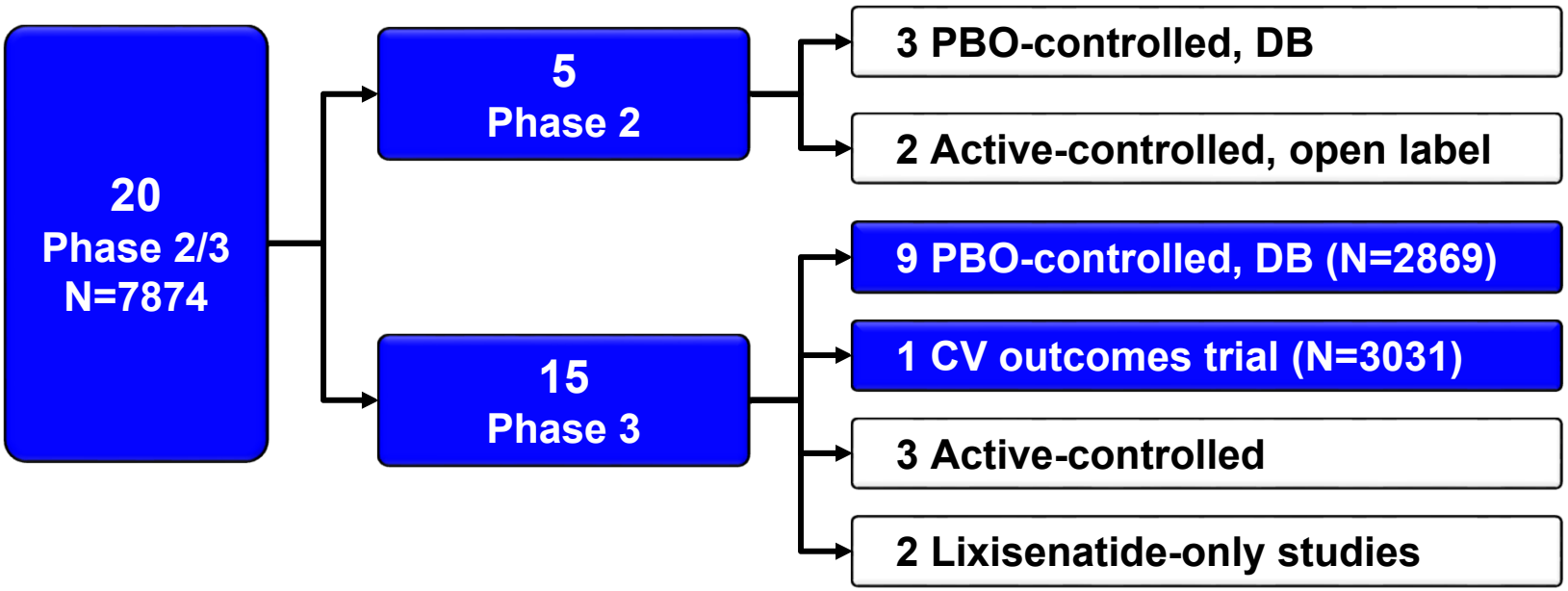
Lantus Well-Established Safety Profile

- >37,000 adult patients with diabetes in clinical trials
- ORIGIN confirmed long-term CV safety in >6,000 Lantus-treated patients
- 89 million patient-years post-marketing experience

Overview of Safety Presentation

- General safety: Lixisenatide and iGlarLixi
- GLP-1 agonist class events of interest
- Key findings from ELIXA

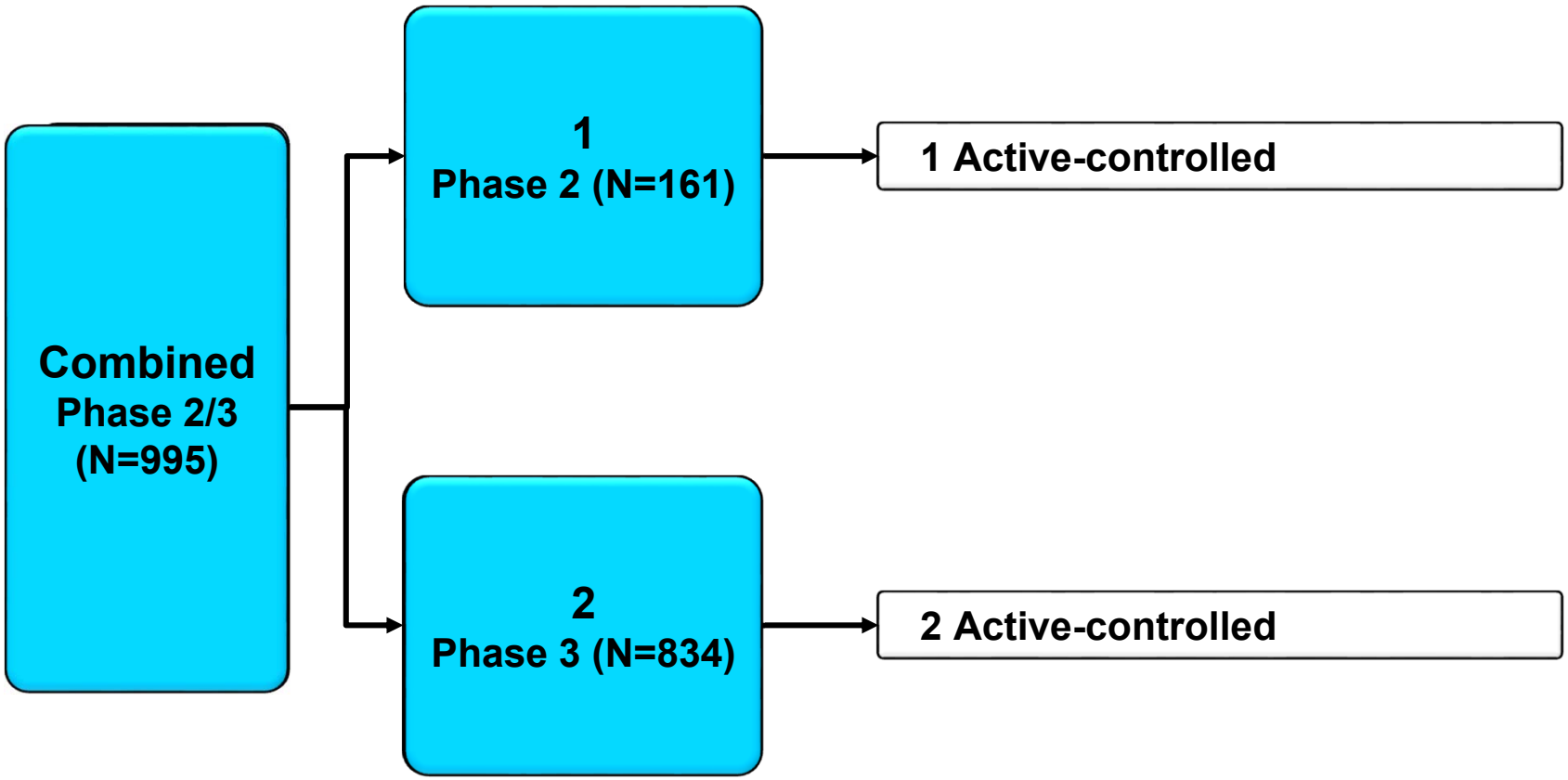
Extensive Safety Population Included >7800 Lixisenatide-Treated Patients



- >10,000 patient-years cumulative exposure to Lixisenatide in Phase 2/3 program

N = Lixisenatide-treated patients

Safety Population: iGlarLixi-Treated Patients



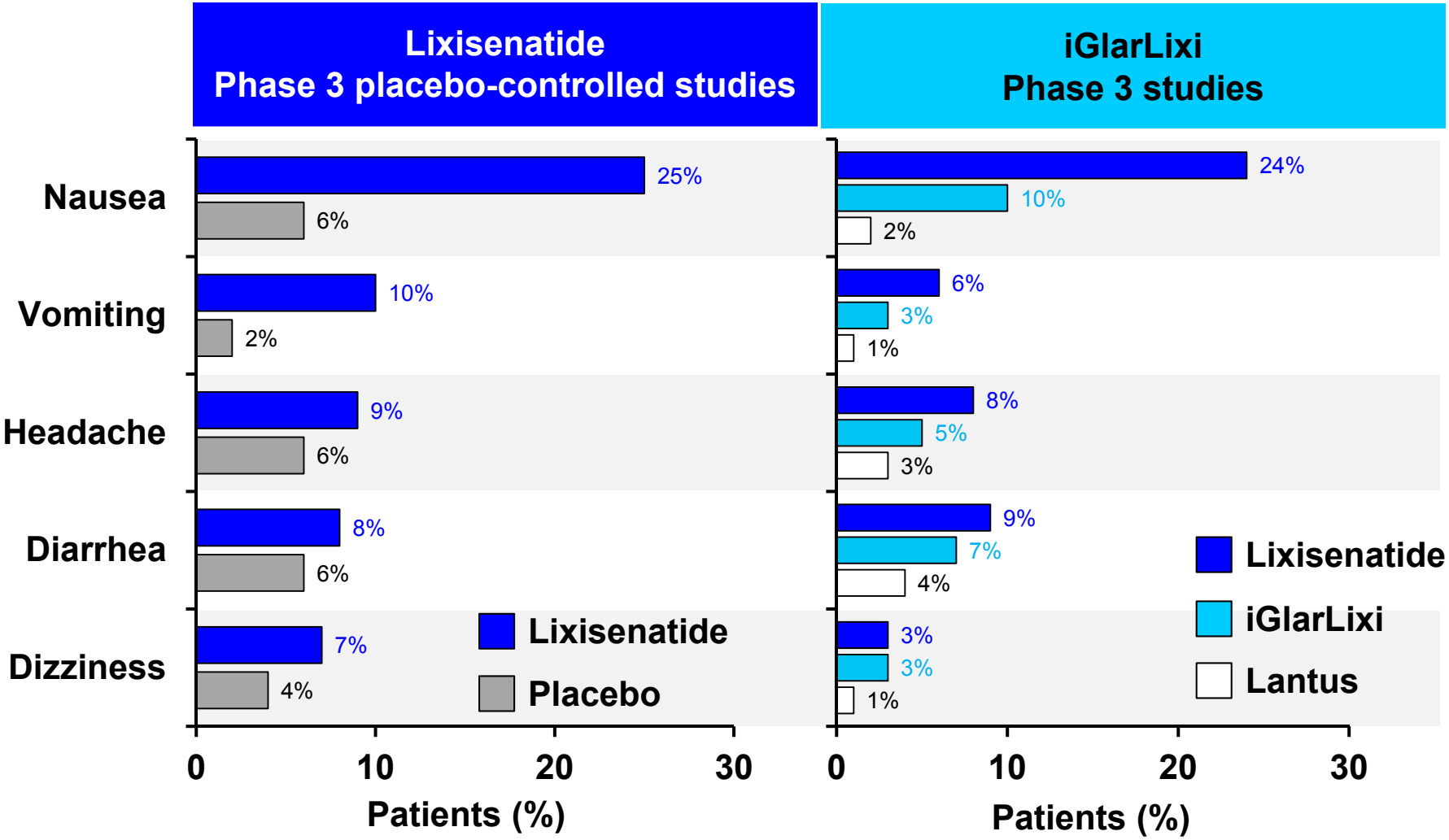
N = iGlarLixi-treated patients

Overview of Adverse Events

Phase 3 placebo-controlled studies	Lixisenatide		iGlarLixi		
	Main treatment period		Study 404 + 405		Study 404
	Lixisenatide (N=2869)	Placebo (N=1639)	iGlarLixi (N=834)	Lantus (N=832)	Lixi (N=233)
Any AE	**70%**	**62%**	**55%**	**50%**	**67%**
AE leading to discontinuation	**7%**	**3%**	**3%**	**1%**	**9%**
GI Events*	4%	0.5%	1%	0.1%	5%
Serious AE	**3%**	**4%**	**5%**	**4%**	**4%**
Deaths	**0.5%**	**0.7%**	**0.4%**	**0.7%**	**0.4%**

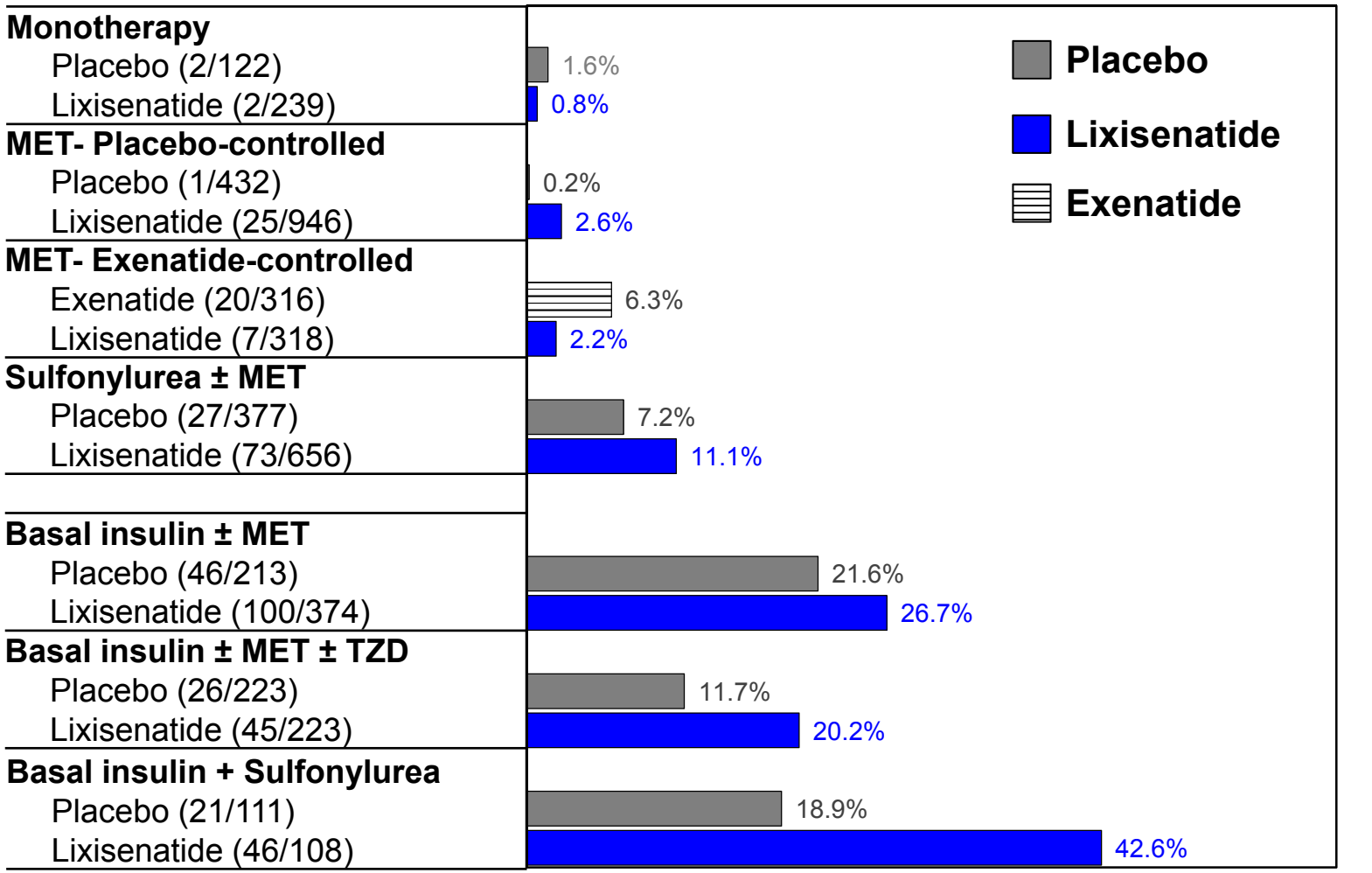
* MedDRA Gastrointestinal disorders System Organ Class (SOC)

Nausea and Vomiting Among Most Frequent Events with Lixisenatide



Event reported in ≥ 6% in any treatment arm and Lixisenatide > comparator; hypoglycemia excluded

Documented Symptomatic Hypoglycemia with Lixisenatide



Plasma glucose <60 mg/dL
Phase 3 controlled studies, Main (24 wk period)

Documented Symptomatic Hypoglycemia: iGlarLixi Phase 3 Studies 404 & 405

Study 404	iGlarLixi (N=469) %	Lantus (N=467) %	Lixisenatide (N=233) %
Documented symptomatic hypoglycemia*	25.6	23.6	6.4
Events per patient-year	1.44	1.22	0.34

Study 405	iGlarLixi (N=365) %	Lantus (N=365) %
Documented symptomatic hypoglycemia*	40.0	42.5
Events per patient-year	3.03	4.22

*Plasma glucose ≤ 70 mg/dL

Overview of Safety Presentation

- General safety: Lixisenatide and iGlarLixi
- GLP-1 agonist class events of interest
- Key findings from ELIXA

Adverse Events of Interest: Findings Similar to GLP-1 Agonist Class

- GLP-1 agonist class events of interest
  - GI events
  - Hypoglycemia
  - Injection site reactions
  - Pancreatitis
  - Potential for thyroid malignancy
  - Allergic reactions

Allergic Reaction Assessment Committee (ARAC)

- Prospective, standardized and blinded adjudication
- Adjudication process
  - Confirm and categorize allergic events
  - Grade event severity
  - Assess relationship to treatment

ARAC Case Adjudication: Pre-Specified Allergic Diagnoses

ARAC Diagnoses category	Definition
Urticaria (hives)	Papillary or dermal lesion, strictly located to skin, transitory (<24 hours)
Angioedema	Papillary or dermal lesion possibly involving mucosae, transitory (24 to 48 hours)
Anaphylactic reaction	Skin or mucosal lesion of acute onset associated with at least 1 other organ involved (respiratory, GI, vascular, etc.)
Anaphylactic shock	Diagnosis of anaphylaxis had been made and a symptomatic drop in blood pressure had occurred
Other	Allergic diagnosis not meeting other defined categories

Drug-Related Allergic Reactions Infrequent

	Phase 2/3 controlled clinical trials			
	Lixisenatide (N=7312)		All comparators (N=6057)	
	n	%	n	%
Suspected allergic event	283	**3.9**	146	**2.4**
Confirmed allergic event	99	**1.4**	50	**0.8**
Possibly related allergic reaction	29	**0.4**	9	**0.1**
Urticaria (hives)	11	**0.2**	6	**<0.1**
Anaphylactic reaction	9	**0.1**	0	**0**
Other (non-serious cutaneous)	6	**<0.1**	2	**<0.1**
Angioedema	5	**<0.1**	2	**<0.1**
Anaphylactic shock	1	**<0.1**	0	**0**

- One anaphylactic reaction reported in Lixisenatide arm of iGlarLixi Study 404

Phase 2/3 clinical trials excluding ACT6011, which was completed prior to ARAC initiation

Adjudicated Anaphylactic Reaction or Shock: Lixisenatide and iGlarLixi Programs (1 of 2)

#	SAE	Investigator diagnosis	Case details	Event treatment
1	N	Allergic dermatitis	Itching, eye/tongue swelling, abdominal pain	Antihistamine
2	N	Allergic reaction	Pruritus, injection site erythema, hoarseness, wheeze	Antihistamine
3	N	Allergic reaction	Urticaria, nausea	Antihistamine
4	N	Dermatitis allergic	Pruritus, injection site swelling, erythema	Antihistamine, steroid
5	Y	Anaphylactic reaction	Pruritus, lip/tongue swelling, dyspnea	Antihistamine
6	Y	Angioedema	Lip swelling, dizziness (normal BP)	Antihistamine, steroid
7	Y	Dermatitis allergic	Pruritus, dizziness (normal BP)	Antihistamine, steroid

- Cases did not meet Sampson's or NIAID criteria for anaphylaxis
- Resolved following treatment

Adjudicated Anaphylactic Reaction or Shock: Lixisenatide and iGlarLixi Programs (2 of 2)

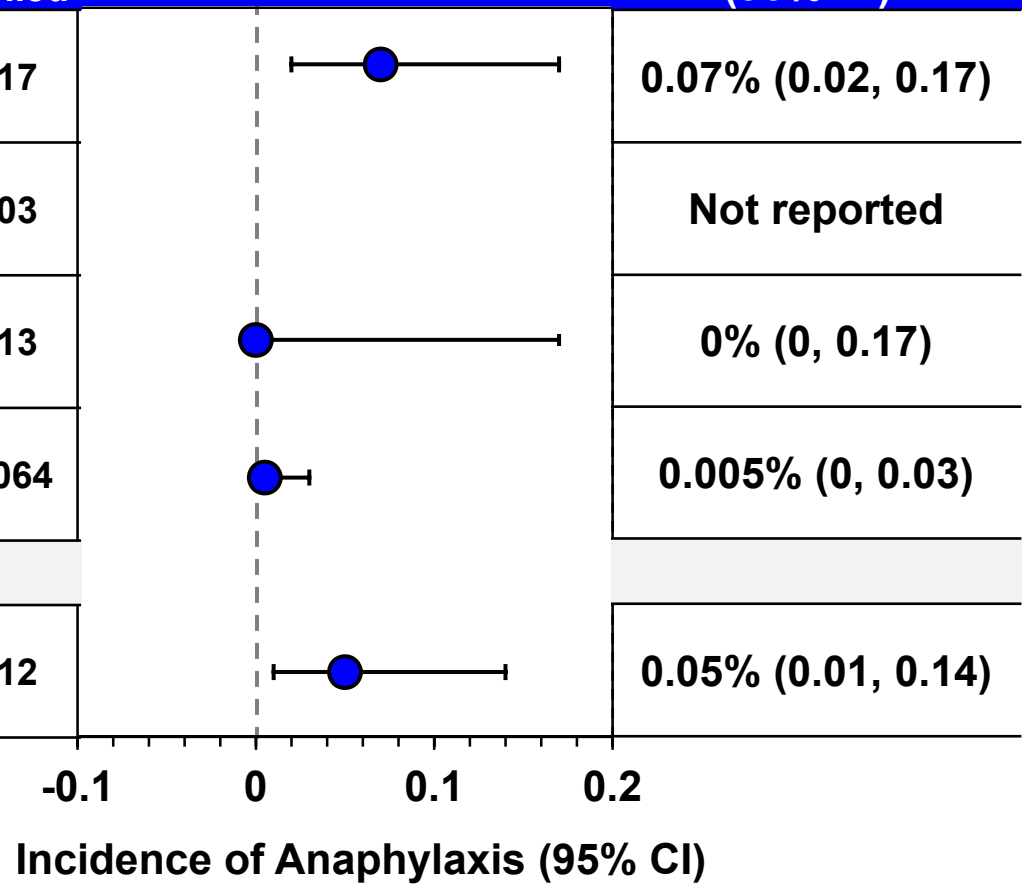
#	SAE	Investigator diagnosis	Case details	Event treatment
8	Y	Allergic shock	Anaphylactoid shock complicated by MI	Steroids
9	Y	Allergic reaction	Angioedema, chest tightness	O_2, epi, antihistamine, steroids
10	Y	Generalized pruritus	Angioedema, wheezing (history of COPD)	O_2, salbutamol, antihistamine
11	Y	Anaphylactic reaction	Dyspnea / mild stridor, rash	Steroids

Literature Review: Anaphylaxis and Hypersensitivity with GLP-1 Agonists

- Assess comparative risk with approved GLP-1 agonists
- Methods
  - Databases: Medline and Embase
  - Search terms: anaphylaxis, hypersensitivity reactions, hypersensitivity, angioedema, allergic reactions
- Focus on publications with adequate sample size to assess rare event
- Lixisenatide hypersensitivity cases captured
  - Using investigator-reported terms

Comparative Incidence of Anaphylaxis: Published GLP-1 Agonists Studies

GLP-1 agonist	Design	Cases	Patients enrolled	Incidence,% (95% CI)*
Exenatide	Postmarketing registry (UK)	5	6717	0.07% (0.02, 0.17)
Liraglutide	Postmarketing registry (UK)	-	2303	Not reported
Dulaglutide	9 pooled Ph 2/3 RCTs	0	2213	0% (0, 0.17)
Exenatide	Postmarketing registry (IT)	1	21,064	0.005% (0, 0.03)
Lixisenatide**	RCTs	4	7312	0.05% (0.01, 0.14)



*Fisher's exact method used to calculate 95% CI
** Investigator reported

Summary of Allergic Reactions with Lixisenatide and iGlarLixi

- Potential for allergic reactions with Lixisenatide and iGlarLixi
- Thorough identification and assessment
  - Event of interest designation
  - ARAC adjudication
- Clinically severe anaphylaxis rare
  - 4 cases in ~9,000 patients treated
  - Findings consistent with published incidence from marketed GLP-1 agonists

Overview of Safety Presentation

- General safety: Lixisenatide and iGlarLixi
- GLP-1 agonist class events of interest
- Key findings from ELIXA

ELIXA: Study Design and Methods

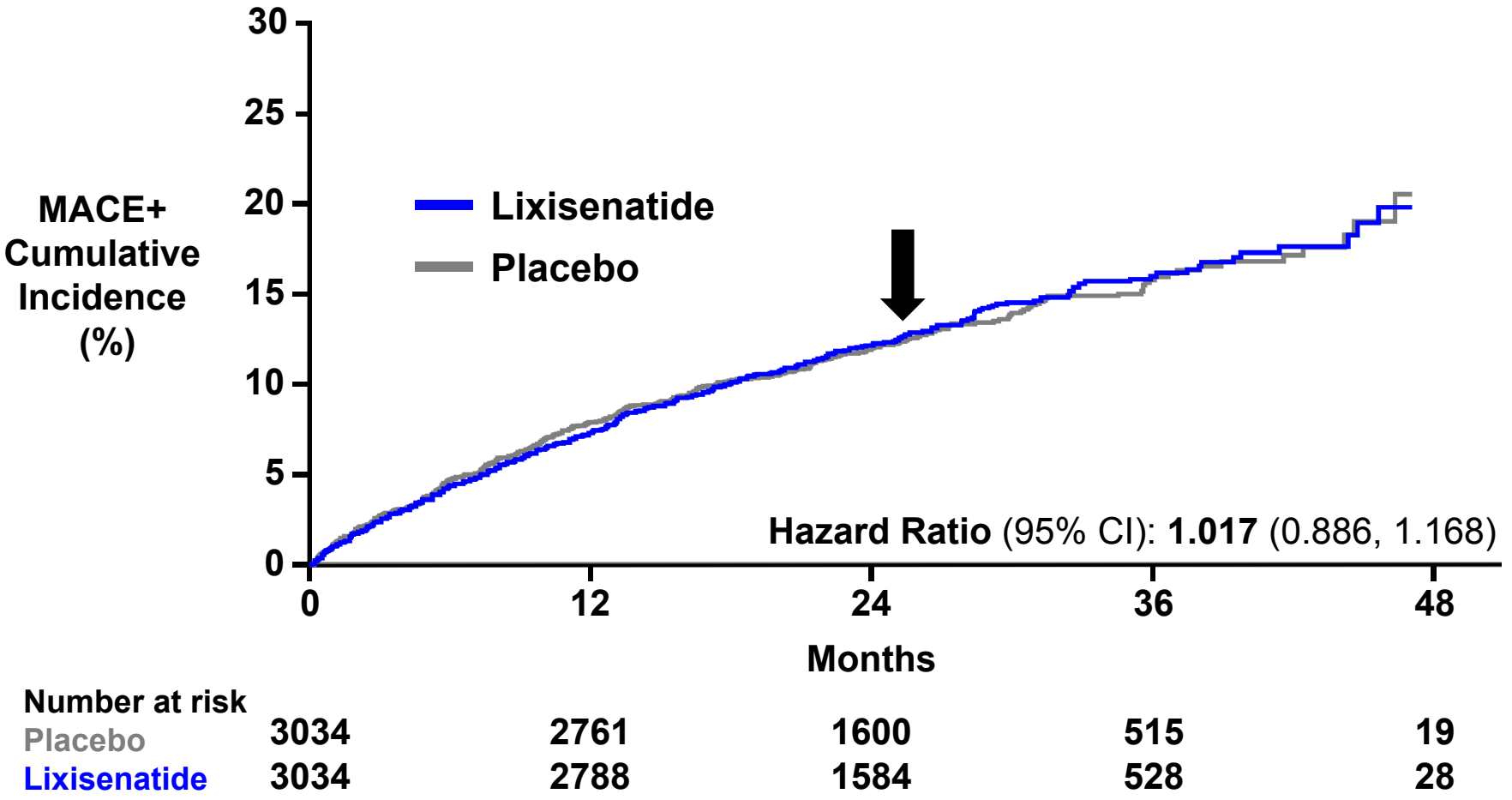
- 1:1 randomized, double-blind, placebo-controlled, event-driven trial
- Designed to demonstrate CV safety of Lixisenatide in high risk type 2 diabetes population
  - All patients with recent (<180 days) documented Acute Coronary Syndrome (ACS)
- Additional glycemic therapy left to investigator's judgment
- Cox proportional hazards model in ITT population

ELIXA: Key Endpoints

Endpoint	
Primary (MACE+)	CV death Non-fatal MI Non-fatal stroke Hospitalization for unstable angina
Secondary endpoints	Any primary endpoint event or hospitalization for heart failure (HF)
	Any primary event, or hospitalization for HF, or coronary revascularization procedure

- Endpoint events adjudicated by independent Cardiovascular Events Adjudication Committee (CAC)

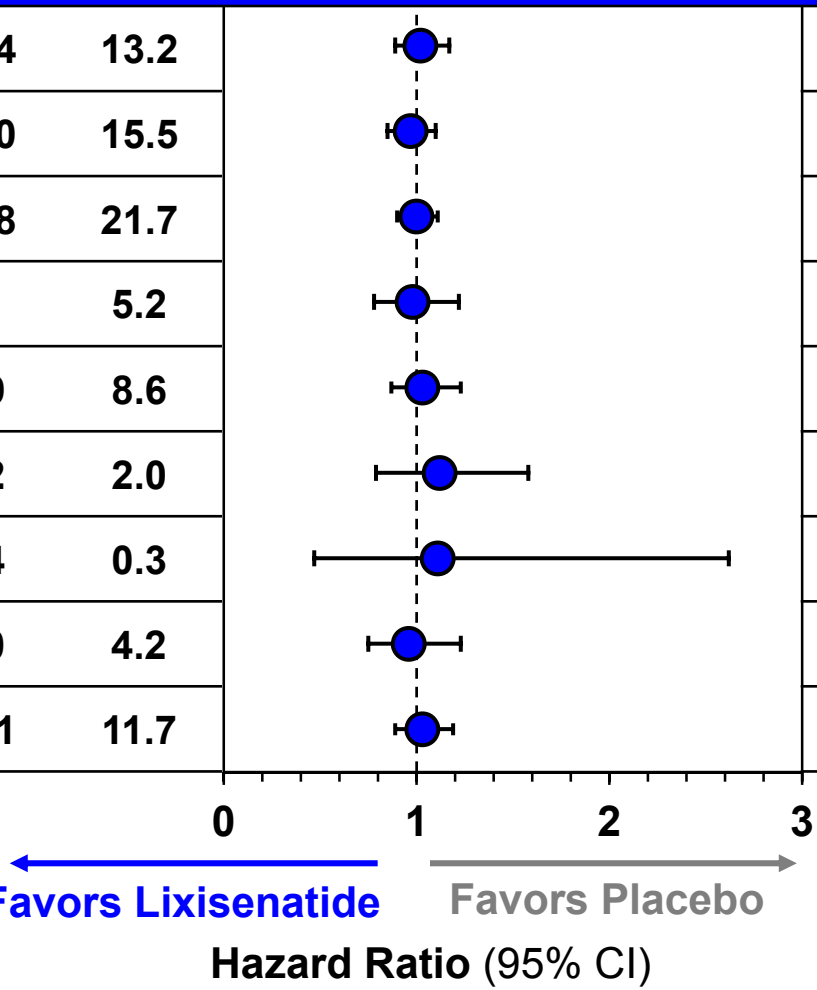
ELIXA: CV Safety Confirmed with Lixisenatide in High-Risk Post-ACS Population



MACE+ = CV death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina

ELIXA: Consistent Effect on All Composite and Individual Components

	Lixi %	PBO %	Hazard Ratio (95% CI)
Primary composite	**13.4**	**13.2**	**1.02** (0.89, 1.17)
Secondary (+HF)	**15.0**	**15.5**	**0.97** (0.85, 1.10)
Secondary (+HF +Revasc)	**21.8**	**21.7**	**1.00** (0.90, 1.11)
CV death	**5.1**	**5.2**	**0.98** (0.78, 1.22)
MI	**8.9**	**8.6**	**1.03** (0.87, 1.23)
Stroke	**2.2**	**2.0**	**1.12** (0.79, 1.58)
Hosp. for unstable angina	**0.4**	**0.3**	**1.11** (0.47, 2.62)
Hosp. for heart failure	**4.0**	**4.2**	**0.96** (0.75, 1.23)
Coronary revascularization	**12.1**	**11.7**	**1.03** (0.89, 1.19)



Post-Marketing Risk Management Plan

Risk Communications

- For HCPs & pharmacists
  - US prescribing information
  - Product training materials / support
- For patients
  - Instructions for use
  - Medication guide
  - Patient support program

Risk Characterization

- Pharmaco-epidemiology study

Summary of Safety Findings

- Well-characterized safety profile
  - Extensive development program for Lixisenatide
  - Established safety of Lantus
- Comparable to other members of GLP-1 agonist class
  - Mild to moderate GI events; lessened with iGlarLixi
  - Limited risk for hypoglycemia
- Rare instances of severe allergic reactions
- No increased CV risk in high-risk post-ACS population
- Risks appropriately managed with post-marketing surveillance and proposed risk management plan

FDA Points to Consider

René Belder, MD

Global Project Head Lixisenatide and iGlarLixi

Sanofi

Overview

- Contribution of Lixisenatide to iGlarLixi across entire dose range
- Lantus titration algorithm and dose cap
- Effect of dose decrease upon switching from insulin or transitioning to Pen B
- Safe self-administration with SoloStar® pen

Contribution of Lixisenatide to iGlarLixi Across Entire Dose Range

iGlarLixi Titrated According to Patients' Needs

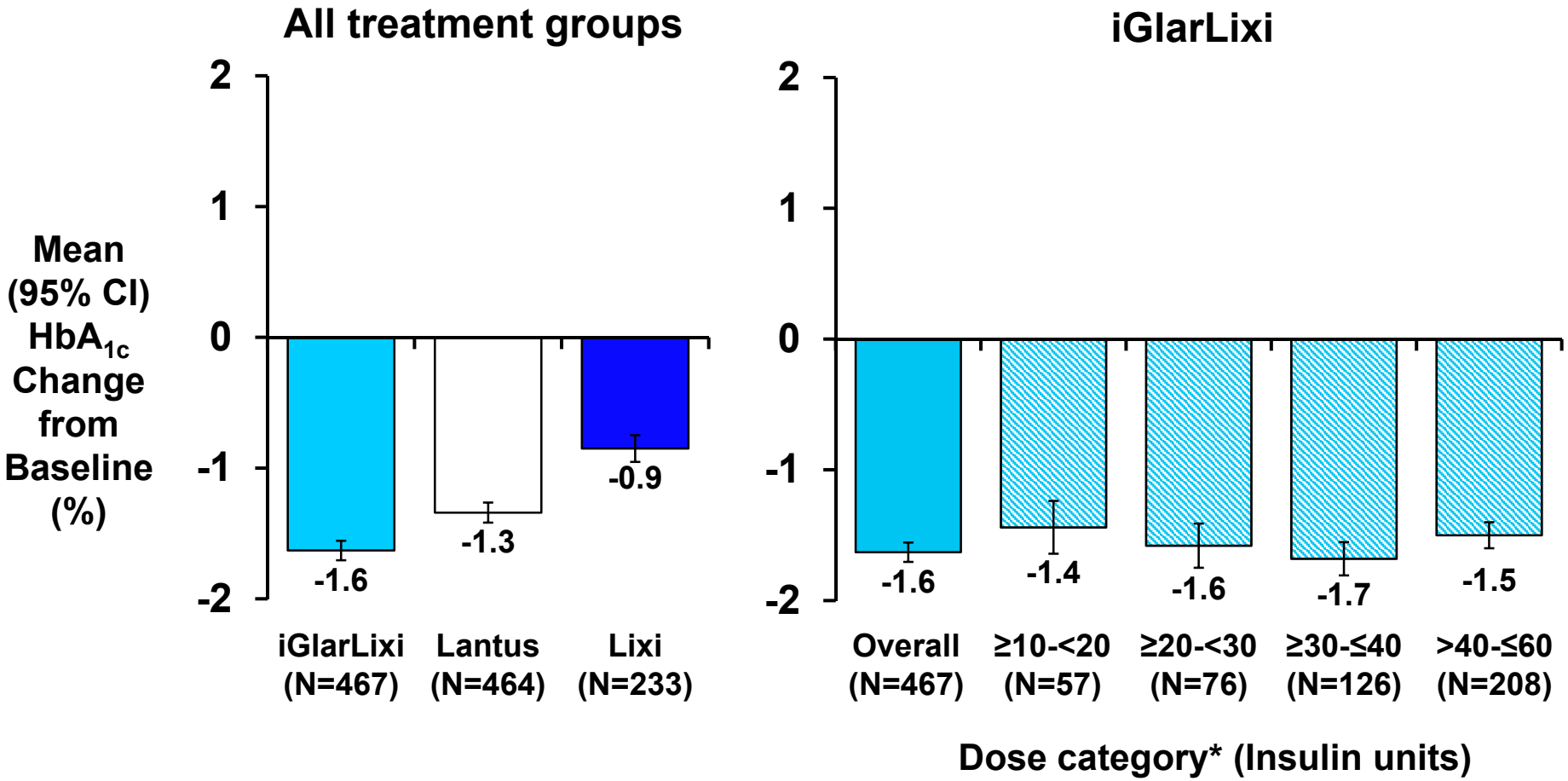
- Randomization not feasible
- Assess pharmacodynamic effects across end-of-study dose categories
- Examined effects on
  - HbA_{1c}
  - PPG
  - Weight gain

Study 404: Patient Distribution Across End-of-Study Dose Categories

	Study 404			
	iGlarLixi (N=468)		Lantus (N=466)	
Final Insulin Dose (U)	n	%	n	%
≥ 10 to <20	58	12%	39	8%
≥ 20 to <30	76	16%	96	21%
≥ 30 to ≤ 40	126	27%	117	25%
> 40 to ≤ 60	208	44%	209	45%

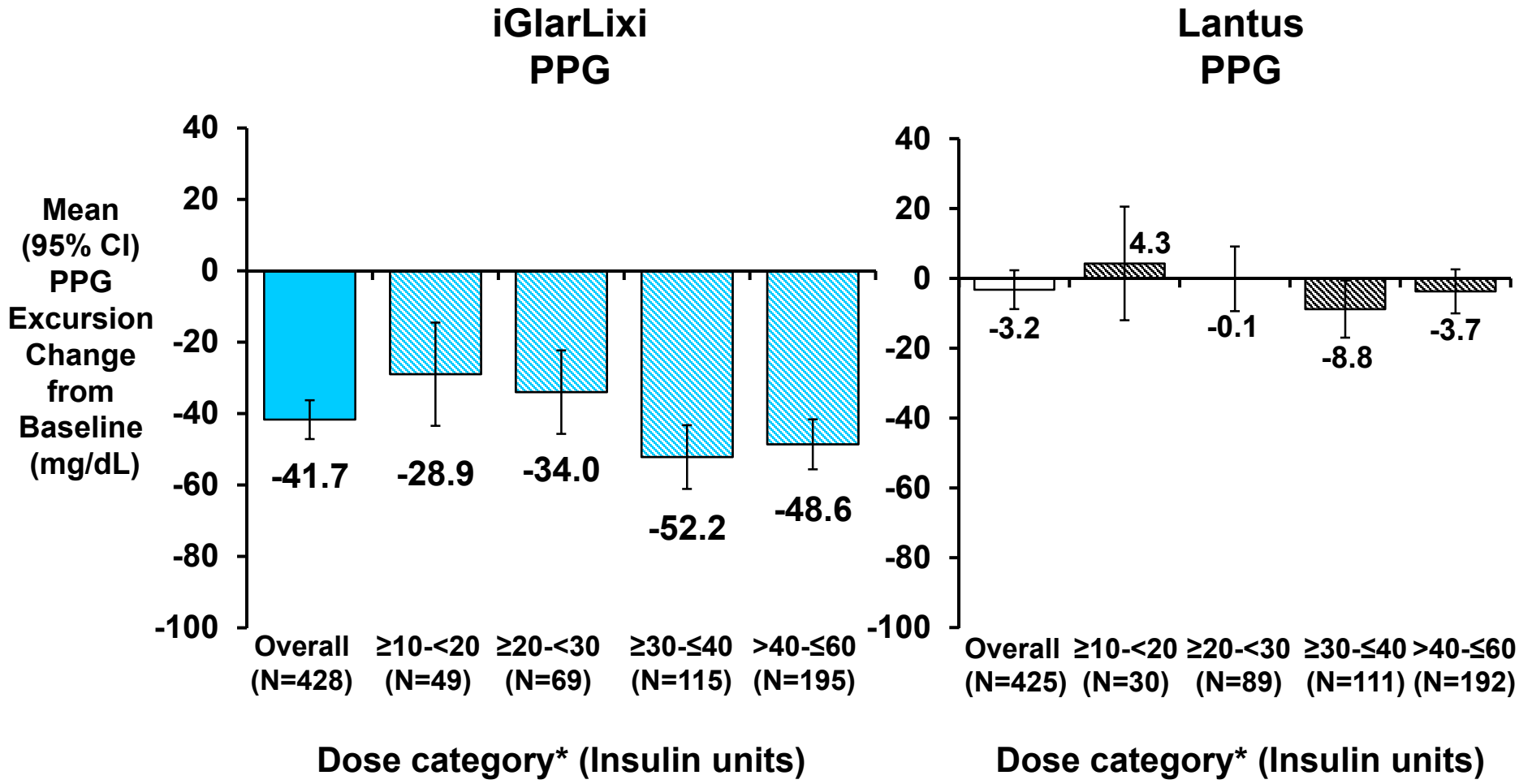
In Lantus arm, 3 patients were on <10U and 2 patients were on >60U

Study 404: Similar HbA_{1c} Effects Across All Dose Categories



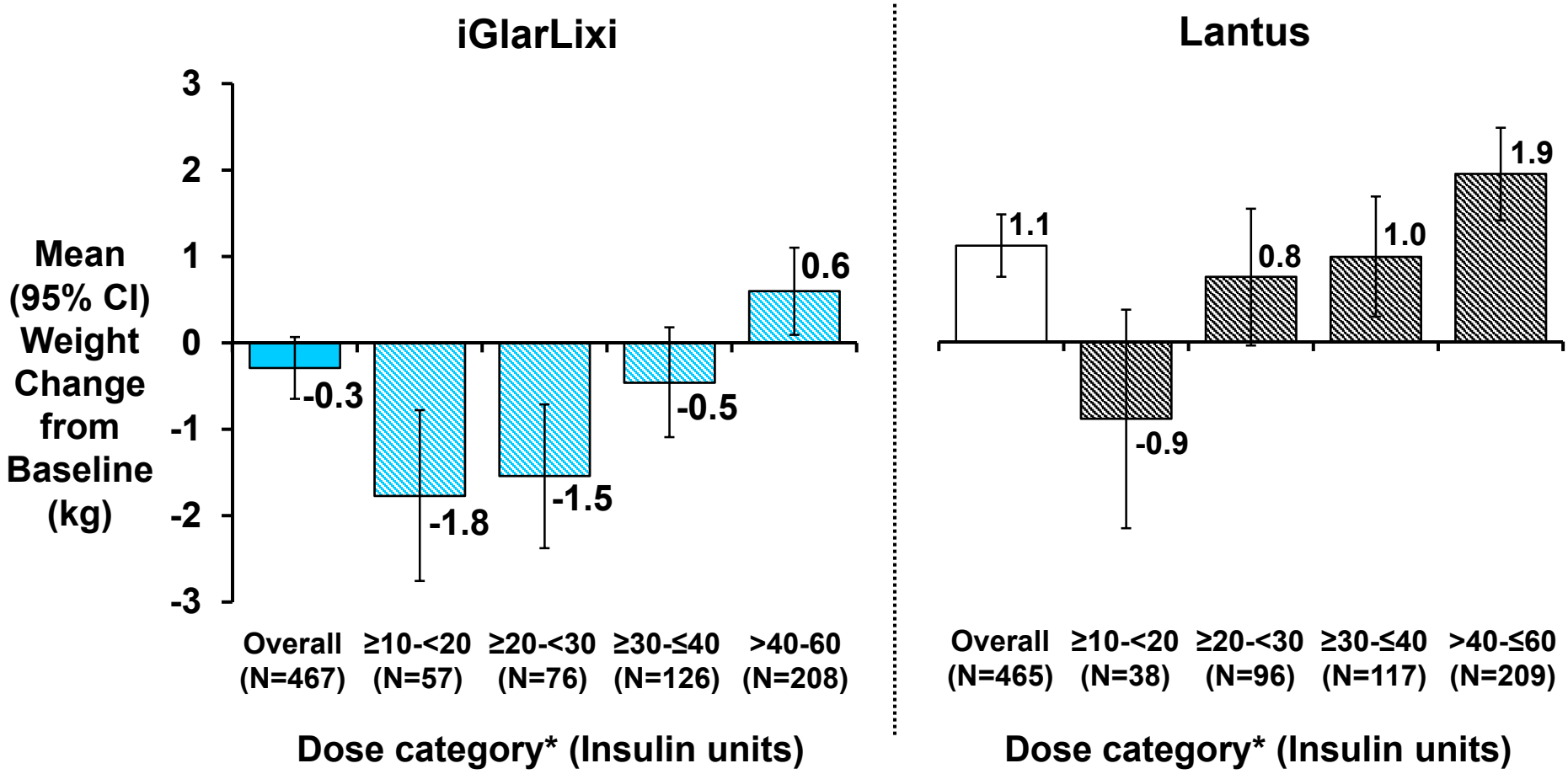
*N = Number of patients with evaluable end of study values

Study 404: Lixisenatide Effect on PPG Present Across All Dose Categories



*N = Number of patients with evaluable end of study values

Study 404: Effect on Weight Across Dose Categories



*N = Number of patients with evaluable end of study values

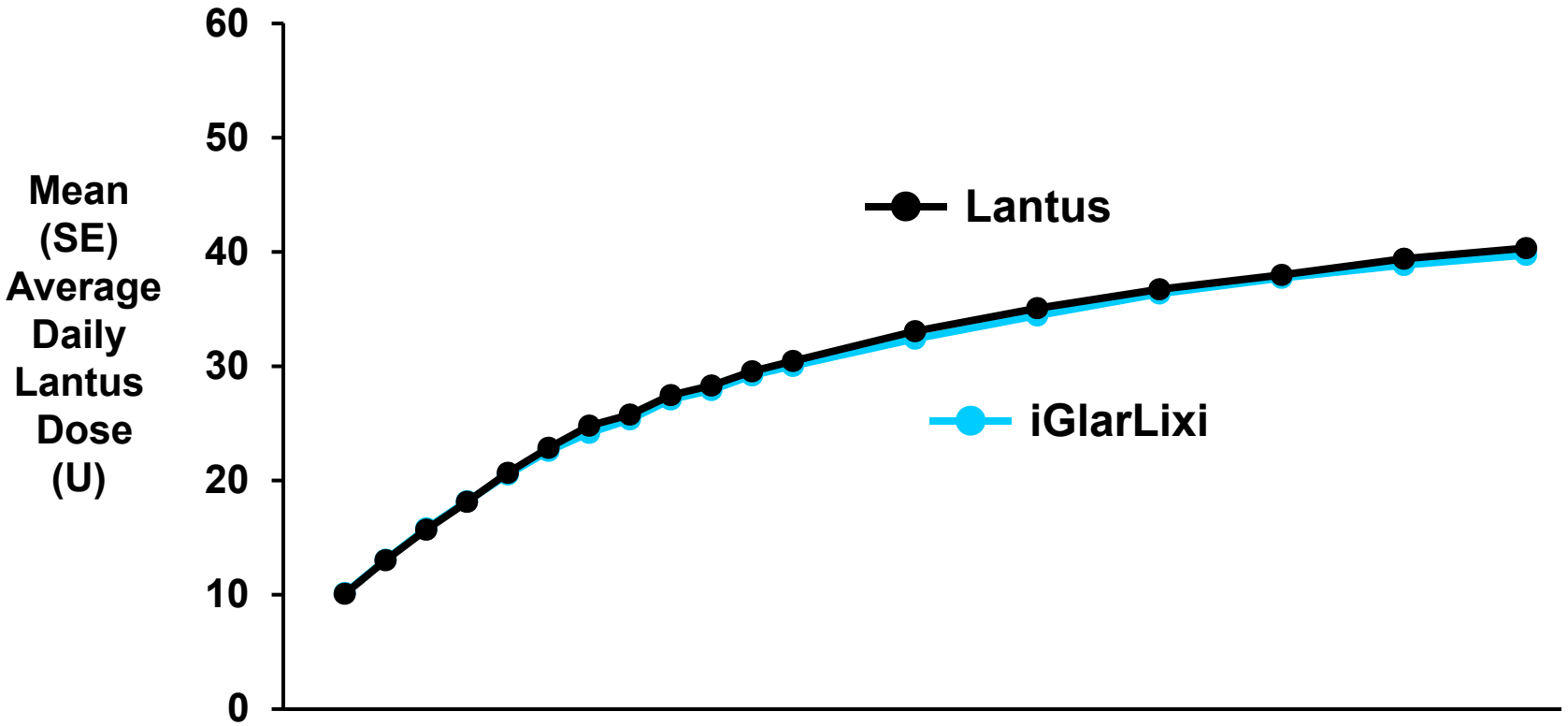
Lantus Titration Algorithm and Dose Cap

Studies 404 and 405: Lantus Titration Algorithm

Median fasting SMPG values (mg/dL)	**Lantus dose adjustments** (U/day)[1]
>140	**+4**
>100 and ≤ 140	**+2**
80-100 (Glycemic target)	**No change**
≥ 60 and <80	**-2**
<60 (or occurrence of ≥ 2 symptomatic hypoglycemic events or one severe hypoglycemic event requiring assistance in prior week)	**-2 to -4** (at discretion of the investigator)

1. Dose adjustment was not to be done more than once weekly

Study 404: Similar Titration in iGlarLixi and Lantus Arms



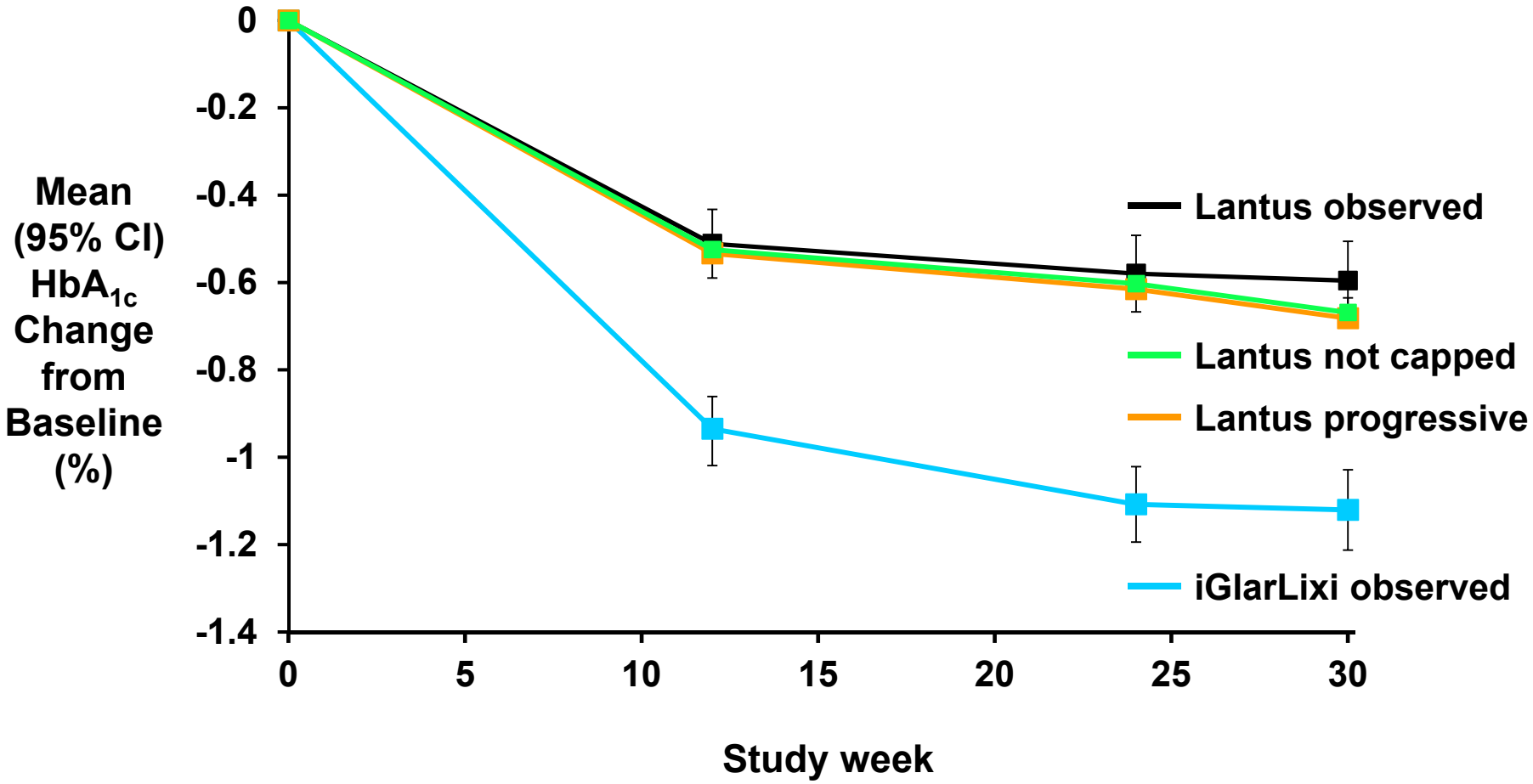
Lantus	457	454	452	421	429	442	447	443	447	440	440
iGlarLixi	462	459	455	433	424	450	449	440	441	438	438

End of Study Glycemic Target Results

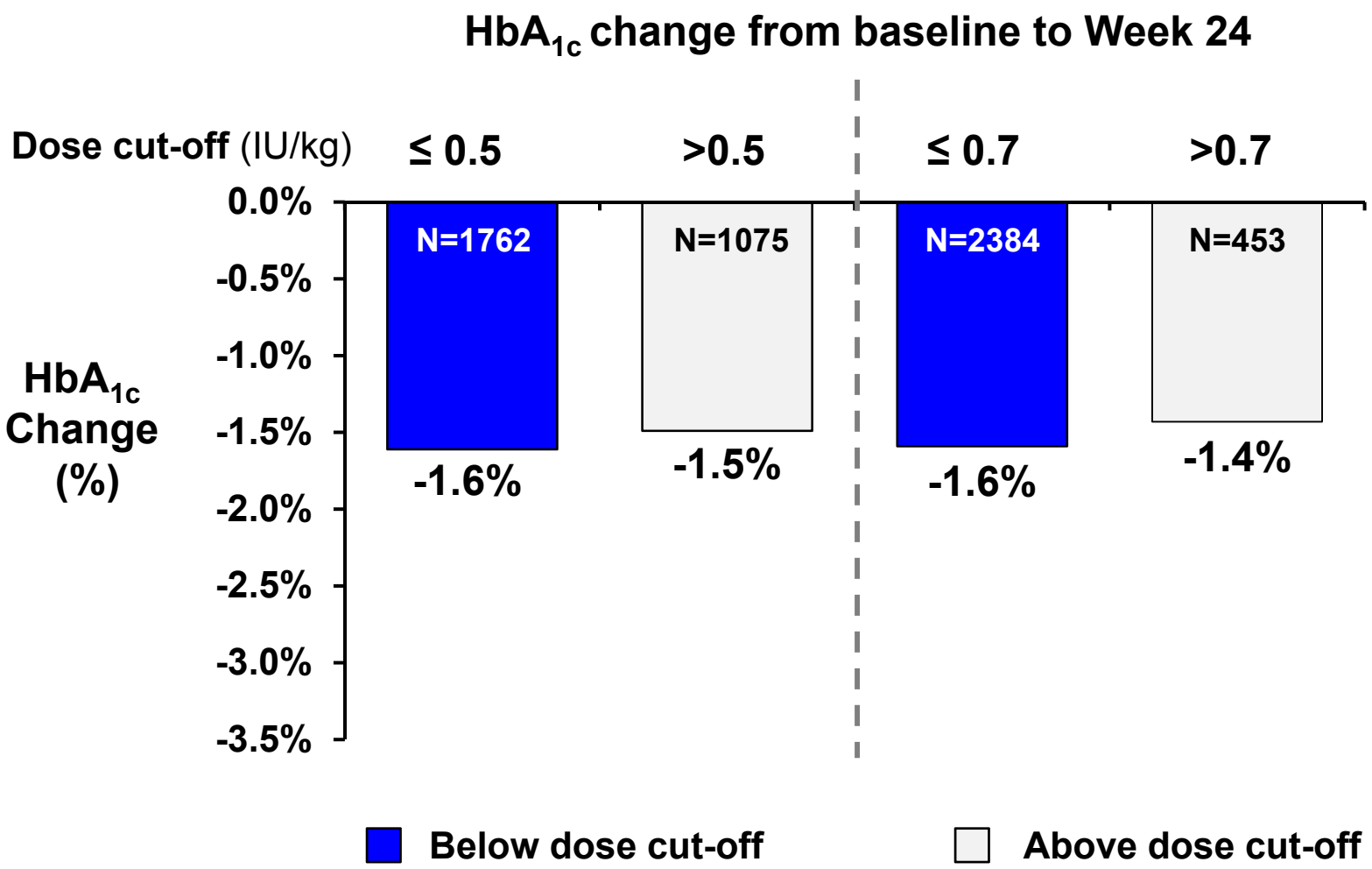
mITT Population	Study 404		Study 405	
	iGlarLixi (N=468)	Lantus (N=466)	iGlarLixi (N=366)	Lantus (N=365)
Fasting SMPG 80-100 mg/dL	45%	40%	41%	38%
FPG ≤ 100 mg/dL*	35%	35%	34%	33%
FPG ≤ 130 mg/dL	79%	71%	67%	66%
HbA_{1c} <7%	74%	59%	55%	30%

*Per protocol

Study 405: No Effect of Dose Cap or Titration Algorithm on Treatment Effect

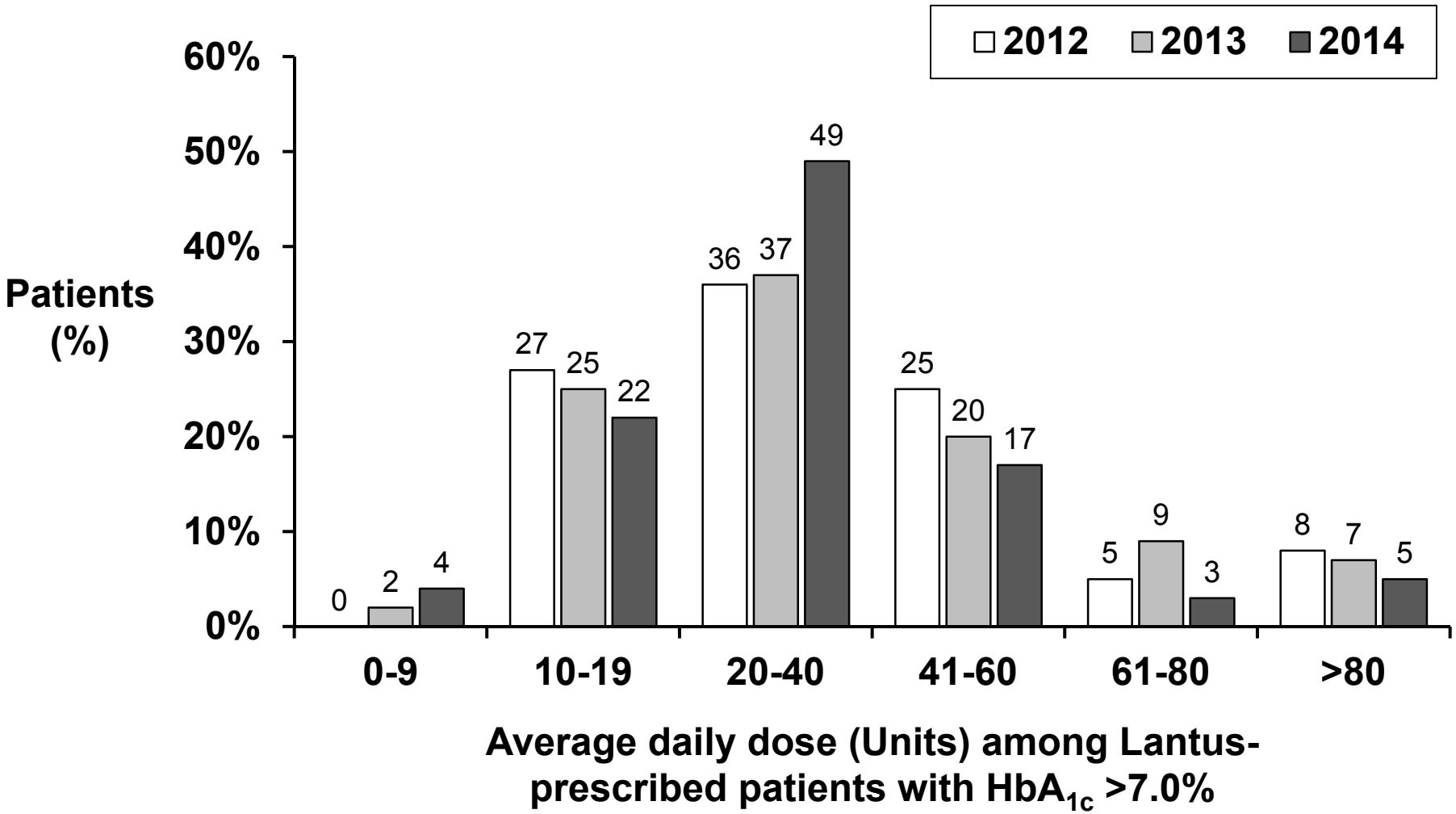


No Apparent HbA_{1c} Benefit from Higher Insulin Dose



Reid (2016)

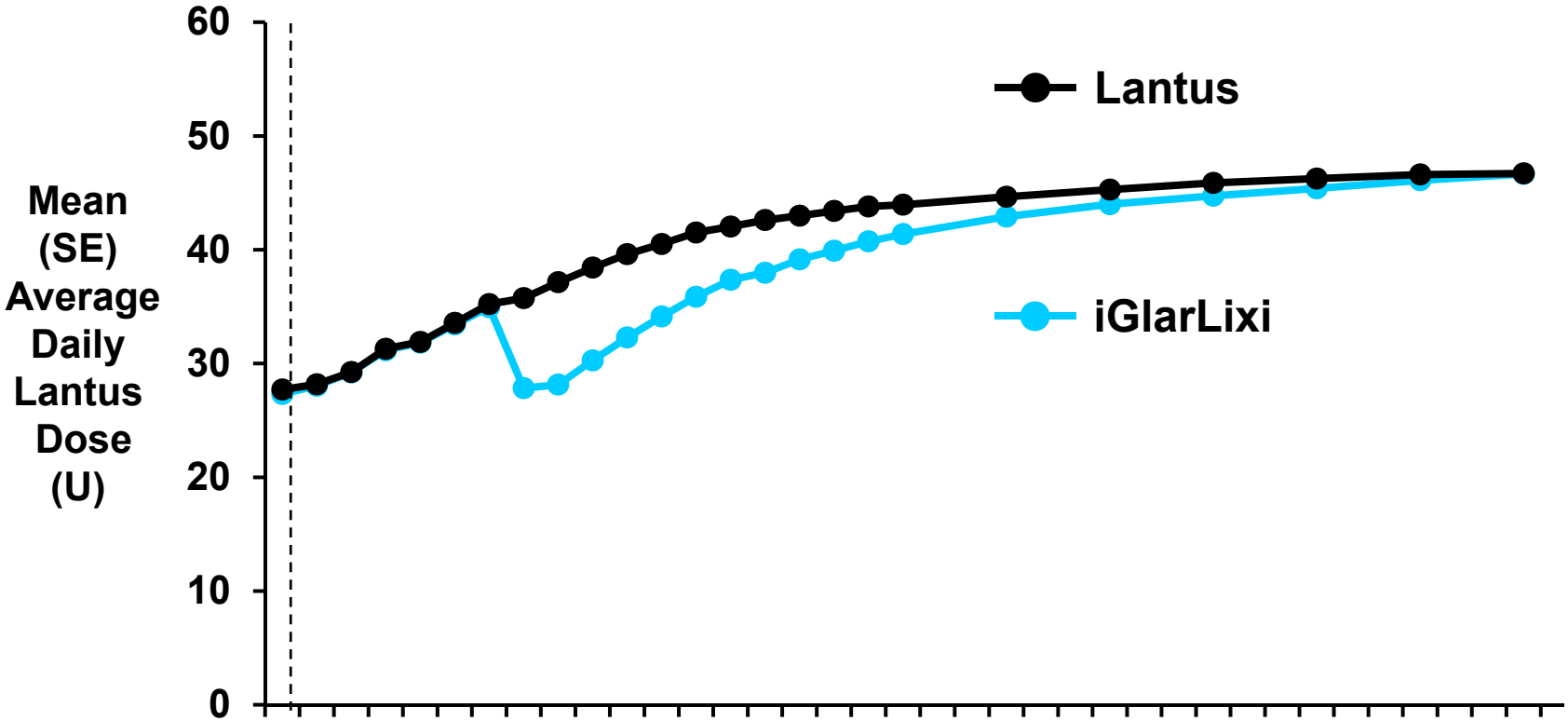
Lantus Dose Range from Both iGlarLixi Pens Supports Majority of Patients



Adelphi Real World DSP (2015)

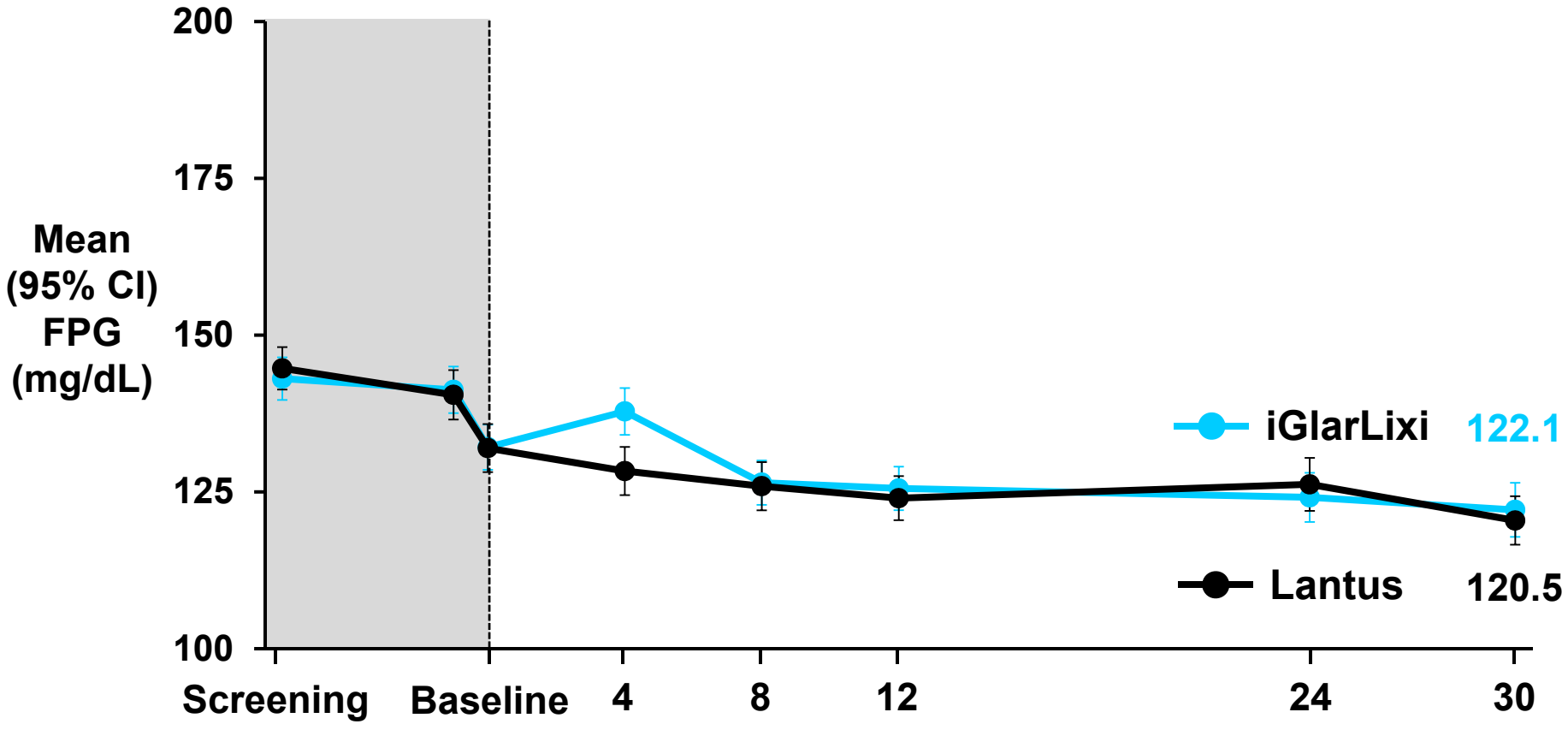
Dose Decrease Upon Switching from Insulin or Transitioning from Pen A to Pen B

Study 405: Temporary Insulin Dose Decrease After Randomization to iGlarLixi



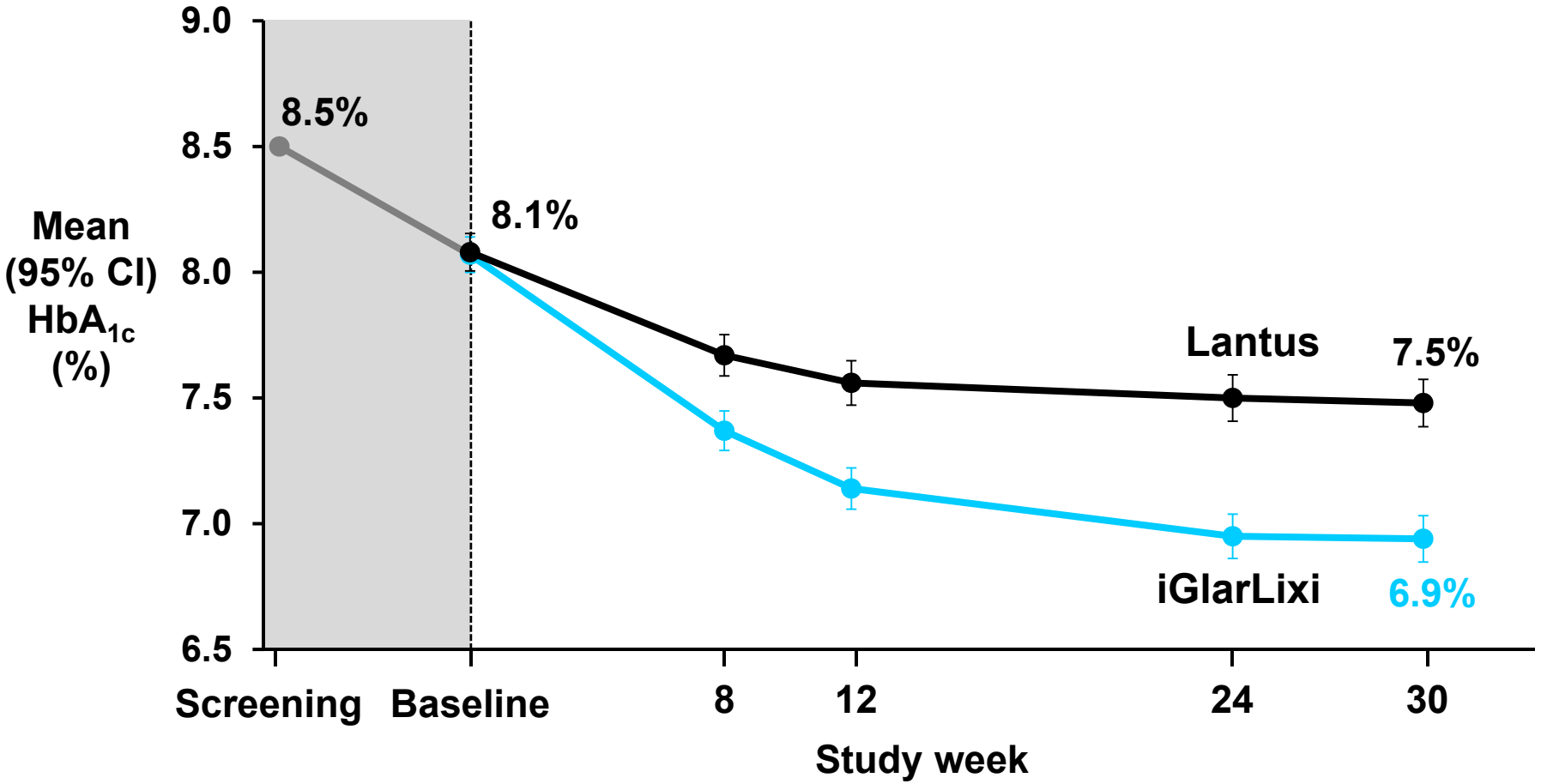
Lantus	365	363	366	359	361	355	357	359	358	355	355	355	353
iGlarLixi	365	364	366	358	356	348	346	337	336	337	337	332	336

Study 405: Transient Increase in FPG



Lantus	362	365	359	353	357	356	349
iGlarLixi	364	366	358	355	355	347	341

Study 405: No Effect of Insulin Dose Decrease on HbA_{1c}



Lantus	365	365	356	360	354	355
iGlarLixi	366	366	357	357	348	346

Reaching Top Dose of Pen A

Pen A

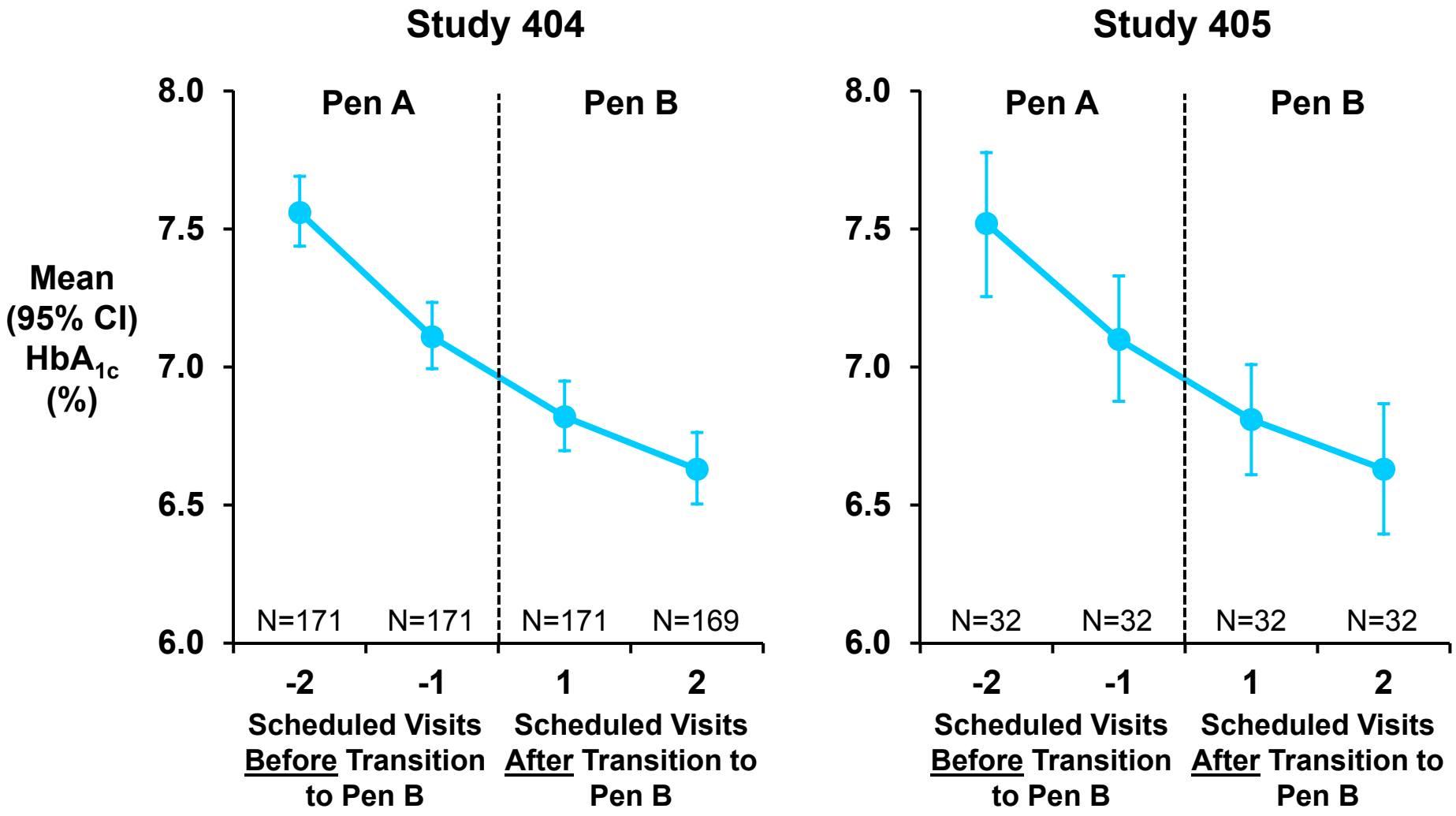
Top dose
40U Lantus / 20 µg Lixi

Transitioning to Pen B

Pen B

Titrated dose
42U Lantus / 14 µg Lixi

No Effect on Glycemic Control When Transitioning from Pen A to Pen B



iGlarLixi Safe Use of Device

2 SoloStar Pens Cover Needs of Broad Range of Patients

2:1 Ratio

3:1 Ratio

SoloStar Pen Platform for iGlarLixi

- Extensive experience with SoloStar pen
- Widely and successfully used in US for many years
- Few pen-related events
  - Similar across treatment groups
- Pen events specific to iGlarLixi
  - 17 patients (~2%, N=834)
  - 22 events (~0.02%, N>100K injections)
  - No associated clinical events

Improvements to Pen for Commercial Use

- Mechanical stops at top dose (40U and 60U)
- Reverse printing below intended dose range
- Kits contain one type of pen
- Instructions for Use
  - Single daily injection of 10 to 40 units or …..30 to 60 units
  - Discard if transitioned to different pen

Results of Human Factors Testing Demonstrated Mitigations Effective

- Participants able to
  - Choose correct pen and dose range
  - Dial and administer correct dose
  - Transition from Pen A to Pen B
  - Store pen properly
- Patient education and support programs
- Device use safe and effective

Summary

- Positive contribution of Lixisenatide across entire dose range
- Treatment effect not influenced by Lantus dose cap or titration algorithm
- No influence of dose decrease on glycemic control
  - After switching from basal insulin
  - After transitioning from Pen A to Pen B
- iGlarLixi SoloStar pen can be used safely and appropriately

Benefit Risk

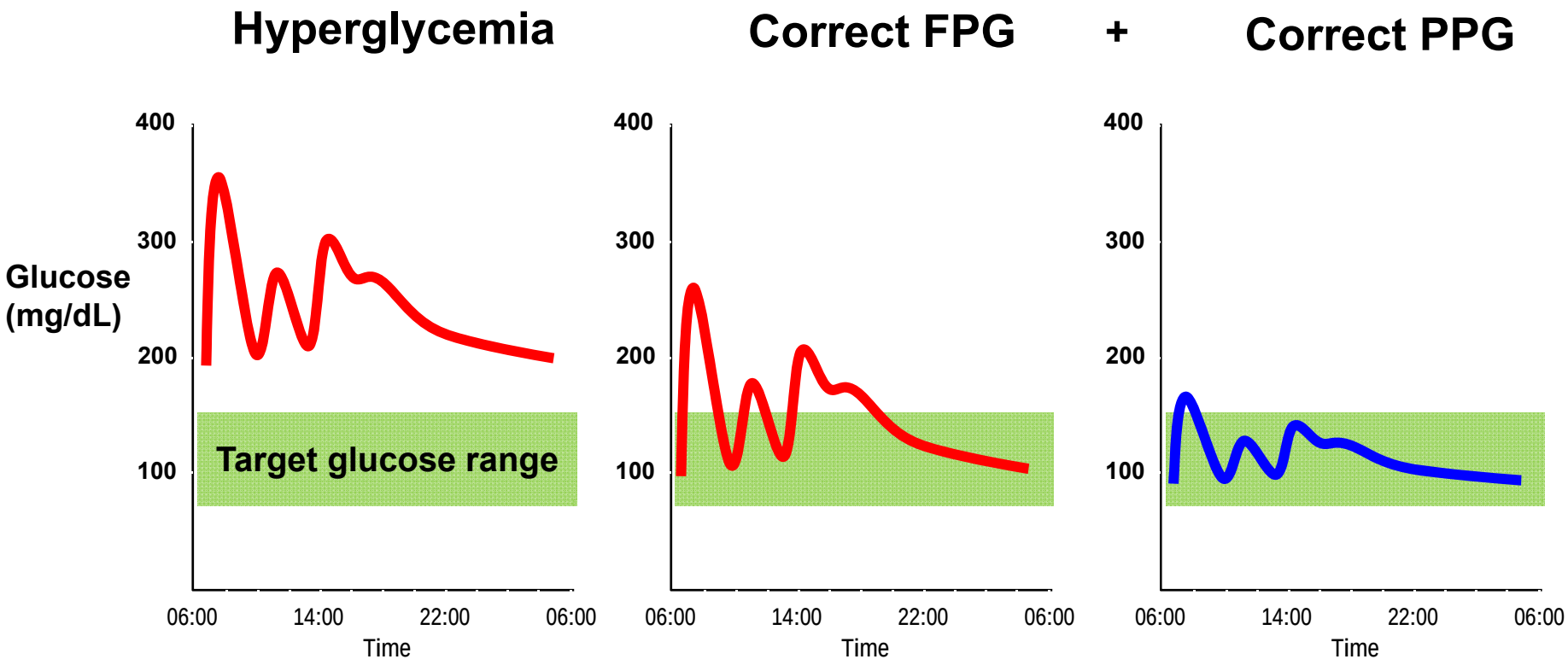
Luigi Meneghini, MD, MBA
Professor of Internal Medicine
University of Texas
Southwestern Medical Center

Falling Short in Our Standard of Practice in Diabetes Care

- ~50% of patients on OADs, HbA_{1c} >7%
- When insulin treatment starts, HbA_{1c} ~9%
- Basal insulin replacement gets ~50% of patients to HbA_{1c} target

Hoerger (2008)

Takes Years to Address Both FPG and PPG and Get HbA_{1c} to Target



HbA_{1c} = FPG + PPG

Lixisenatide Provides Treatment Option that Specifically Lowers PPG

Metformin +	Efficacy	Hypoglycemic risk	Weight change	Side effects
Sulfonylureas	High	Moderate	Gain	Hypoglycemia
Thiazolidinediones	High	Low	Gain	Edema, heart failure, fracture
DPP-4 Inhibitors	Intermediate	Low	Neutral	Arthralgia
SGLT-2 Inhibitors	Intermediate	Low	Loss	GU, dehydration, ketoacidosis
GLP-1 Agonists	High	Low	Loss	GI
Basal Insulin	Highest	High	Gain	Hypoglycemia
Prandial Insulin	High	High	Gain	Hypoglycemia

Adapted from ADA (2016)

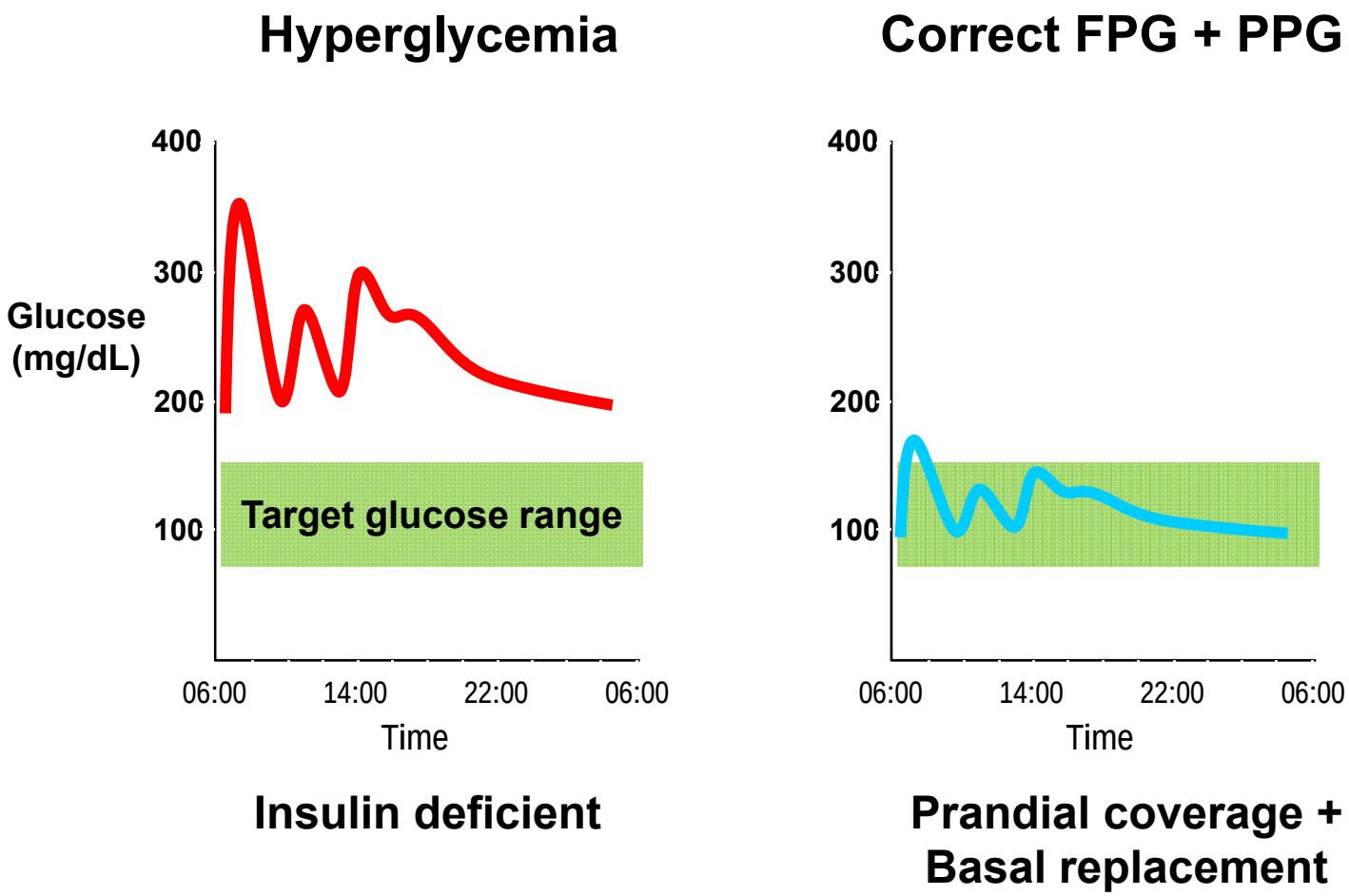
Benefits and Ensuring Safe Use of iGlarLixi

- Simplifying injection regimens
- Bring more patients to HbA_{1c} goal by addressing both FPG and PPG
- No weight gain
- Comparable hypoglycemia with Lantus
- GI tolerability better than Lixisenatide
- CV safety for both components

Additional Clinical Perspective on Use of Pens and Anaphylaxis

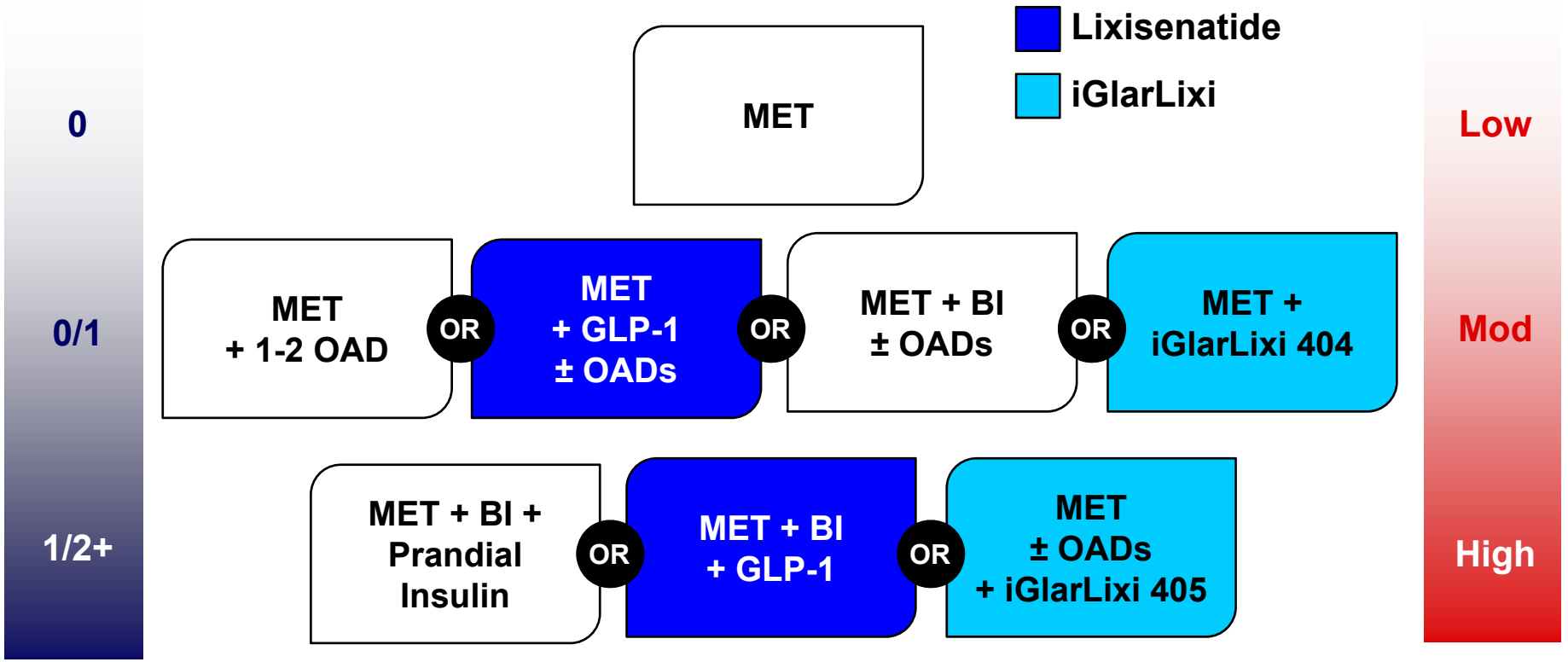
- Dosing range of up to 60U and two drug-to-drug ratios allow flexibility to titrate
  - Balance therapeutic effectiveness with tolerability
- Patients comfortable using SoloStar pen
- Access to robust patient support program
- Low risk of anaphylaxis / comparable to other GLP-1 agonists
  - Risk management plan reasonable

Timely and Robust Correction of Hyperglycemia with iGlarLixi



HbA_{1c} = FPG + PPG

iGlarLixi Fits into Current Treatment Guidelines



BI = Basal Insulin; MET = Metformin
Adapted and modified from ADA

iGlarLixi: Novel Solution to Challenges in Type 2 Diabetes Care

Metformin +	Efficacy	Hypoglycemic risk	Weight change	Side effects
Sulfonylureas	High	Moderate	Gain	Hypoglycemia
Thiazolidinediones	High	Low	Gain	Edema, heart failure, fracture
DPP-4 Inhibitors	Intermediate	Low	Neutral	Arthralgia
SGLT-2 Inhibitors	Intermediate	Low	Loss	GU, dehydration, ketoacidosis
GLP-1 Agonists	High	Low	Loss	GI
Basal Insulin	Highest	High	Gain	Hypoglycemia
Prandial Insulin	High	High	Gain	Hypoglycemia
iGlarLixi	Higher than basal insulin	Comparable to basal insulin	Neutral/ Loss	GI Mild

Adapted and modified from ADA (2016)

Lixisenatide and iGlarLixi Type 2 Diabetes Mellitus

Endocrinologic and Metabolic Drugs

Advisory Committee

May 25, 2016

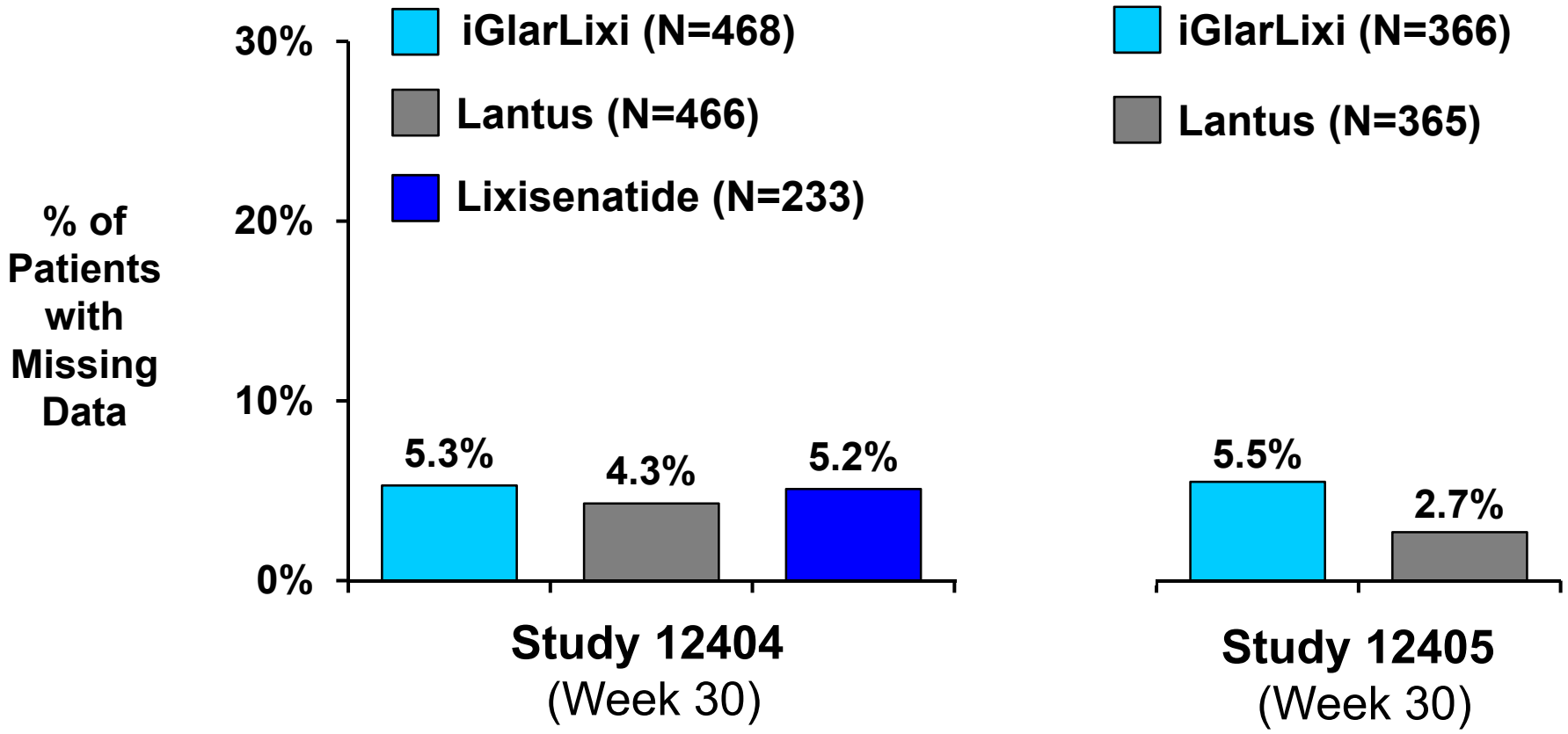
Q&A Slides

AEs by Anti-lixisenatide Antibody (ADA) Status: Phase 3 Placebo-Controlled Studies

Phase 3 Placebo-Controlled Studies (Entire treatment period) MedDRA SOC	Lixisenatide Patients			
	ADA Positive N=2032		ADA Negative N=768	
	%	Rate per 100 PY	%	Rate per 100 PY
Any AE	82.8%	**64.6**	76.6%	**88.6**
Infections And Infestations	43.4%	**33.9**	28.1%	**32.5**
Metabolism And Nutrition Disorders	27.3%	**21.3**	22.0%	**25.5**
Gastrointestinal Disorders	46.2%	**36.1**	46.5%	**53.8**
Nervous System Disorders	27.3%	**21.3**	24.0%	**27.7**

Includes MedDRA SOCs with EAIR > 20 per 100 PY

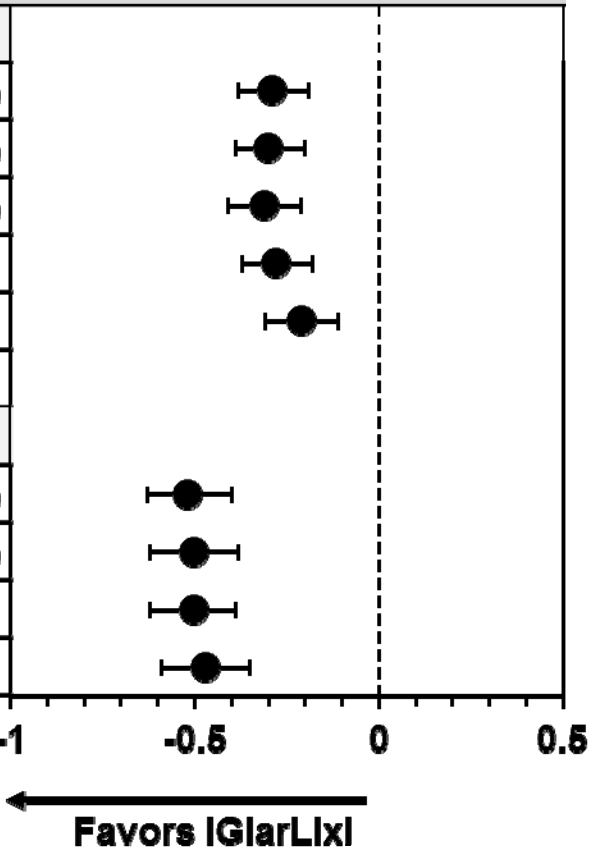
iGlarLixi: Missing Data in HbA_{1c} Change from Baseline at Week 30



mITT Population

Figure 57 - iGlarLixi sensitivity analysis of primary endpoint (iGlarLixi versus insulin glargine)

	iGlarLixi (N)	Lantus (N)	LS Mean Difference (95% CI)
Study 12404			
MMRM (Primary; all post-baseline)	**467**	**464**	**-0.29** (-0.38, -0.19)
MMRM (Before rescue)	**464**	**459**	**-0.30** (-0.39, -0.20)
PMM (Completed Trt vs Not)	**468**	**466**	**-0.31** (-0.41, -0.21)
PMM (MI / Jump to Control)	**468**	**466**	**-0.28** (-0.37, -0.18)
PMM (MI / BOCF-like)	**468**	**466**	**-0.21** (-0.31, -0.11)
Study 12405			
MMRM (Primary; all post-baseline)	**364**	**364**	**-0.52** (-0.63, -0.40)
MMRM (Before rescue)	**362**	**360**	**-0.50** (-0.62, -0.38)
PMM (MI / Jump to Control)	**366**	**365**	**-0.50** (-0.62, -0.39)
PMM (BOCF-like)	**366**	**365**	**-0.47**(-0.59, -0.35)



MMRM: mixed-effect model with repeated measures, PMM: pattern-mixture model, MI: multiple imputation, BOCF: baseline observation carried forward, mITT: modified intent-to-treat

Lixisenatide
Fixed-Dose Pen Injectors

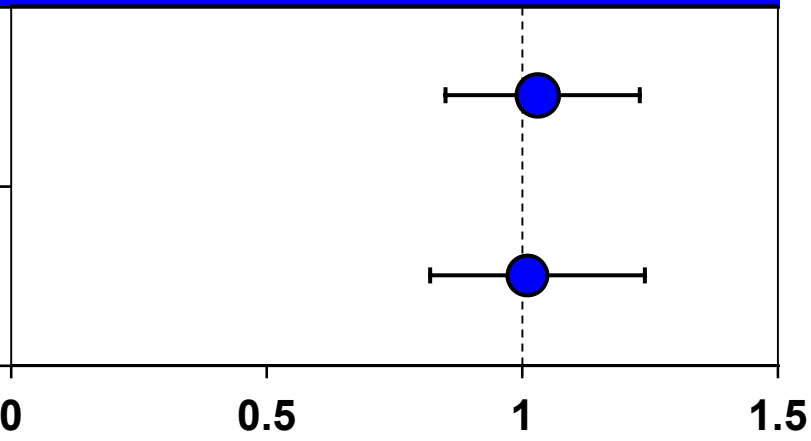
- 2 pens with different concentrations
  - 10 mcg (50 mcg / mL)
  - 20 mcg (100 mcg / mL)

iGlarLixi: GI Events in Study 404 v 405

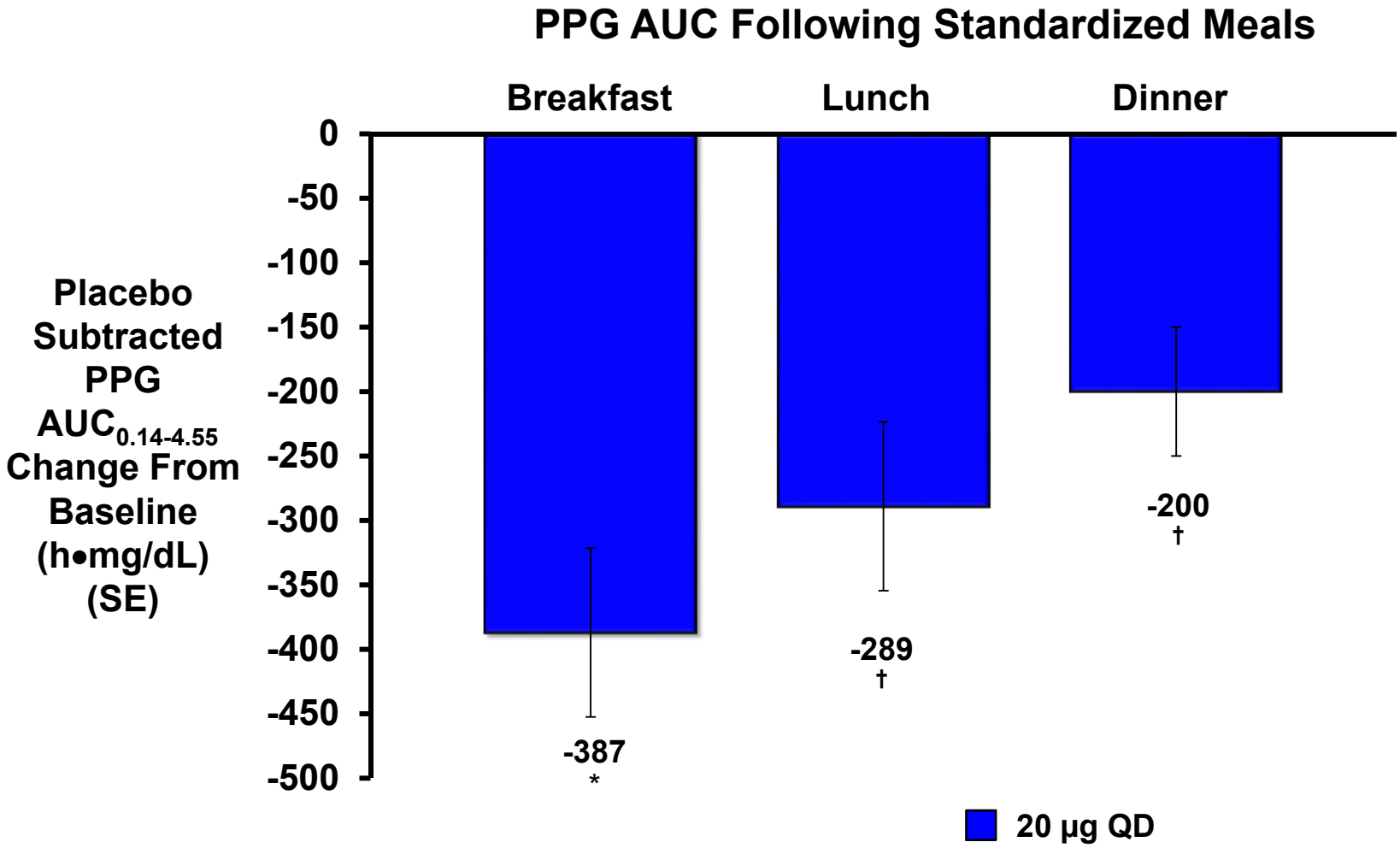
	Study 404			Study 405	
	iGlarLixi	Lantus	Lixi	iGlarLixi	Lantus
N	469	467	233	365	365
Any TEAE	56.9%	48.6%	67.4%	53.4%	52.3%
GI disorders	21.7%	12.6%	36.9%	17.0%	7.9%
Nausea	9.6%	3.6%	24.0%	10.4%	0.5%
Vomiting	3.2%	1.5%	6.4%	3.6%	0.5%
Diarrhea	9.0%	4.3%	9.0%	4.4%	2.7%

ELIXA: MACE+ by Prior Insulin Use

Insulin	Group	Events n/N	HR 95% CI
Yes	Lixisenatide	234/1460	1.03 (0.85,1.23)
	Placebo	223/1430	
No	Lixisenatide	172/1574	1.01 (0.82, 1.24)
	Placebo	176/1604	



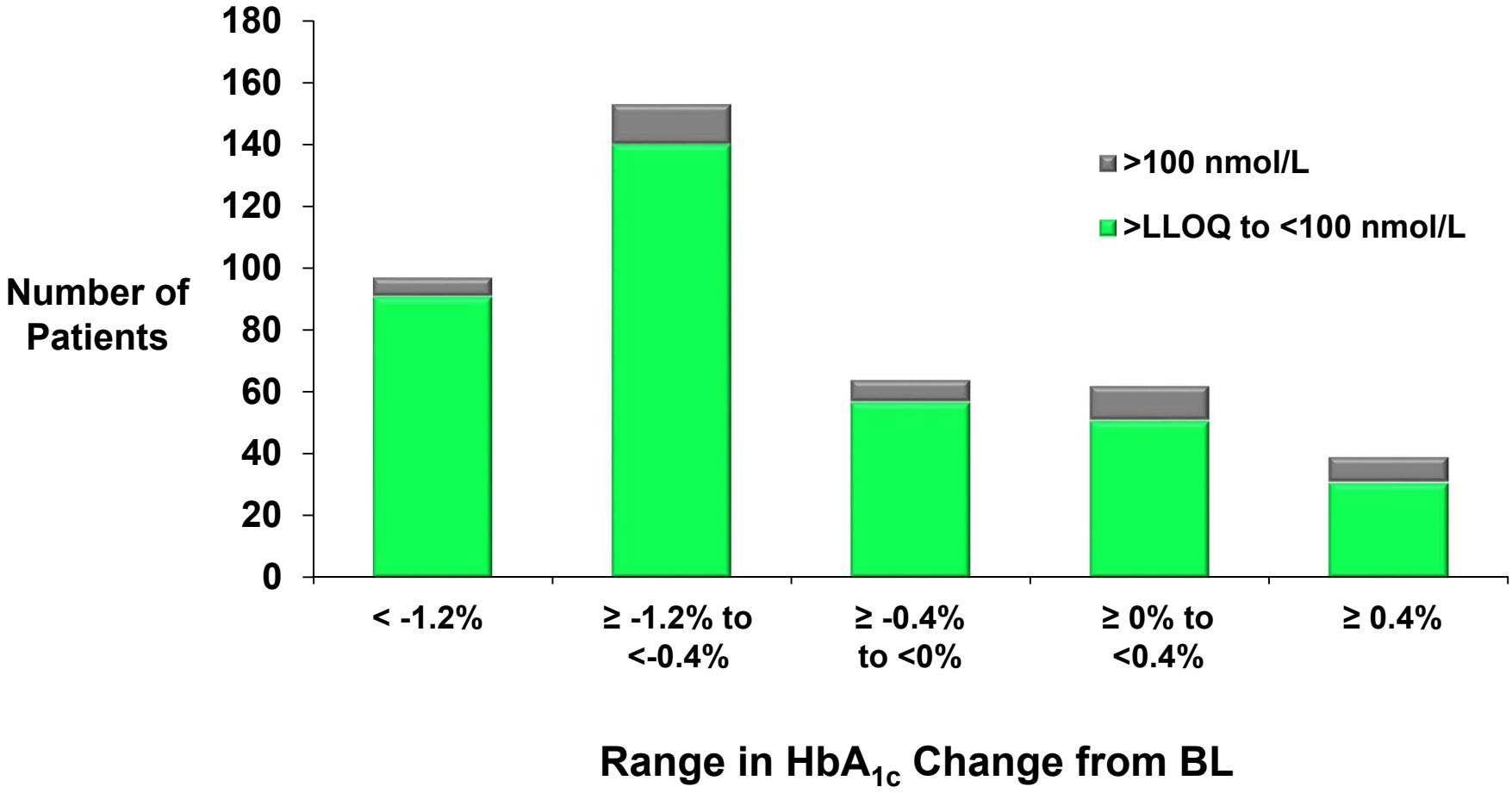
Lixisenatide Reduces PPG Exposure Throughout Day



*p<0.0001, †p<0.005 vs. placebo

Patients with T2D, ascending dose range for 4 weeks, ACT6011

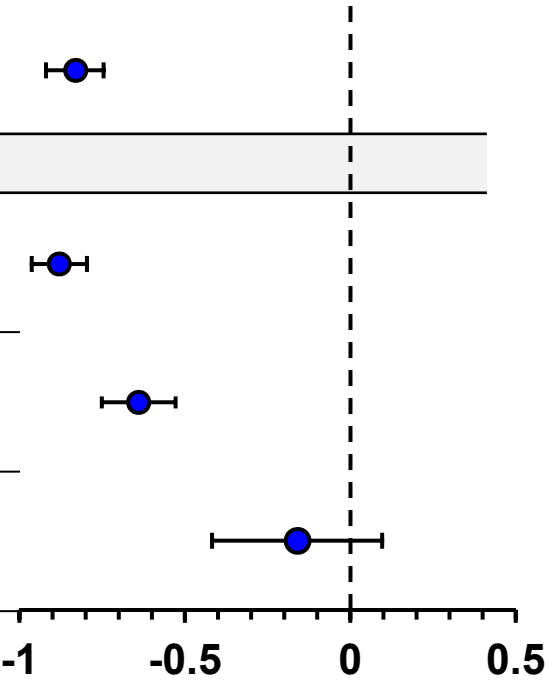
Antibody Categories by Change in HbA_{1c} (Number) from BL to Week 24 - Lixisenatide



AB: anti-lixisenatide antibodies; BL: baseline
Studies included: EFC6014, EFC6015, EFC6016, EFC6017, EFC10743, EFC10781, EFC10887 and EFC11321

Change in HbA_{1c} (%) from Baseline to Week 24 by Antibody Concentration - Lixisenatide

Anti-lixisenatide Antibody Status and Concentration (N=1890)*	N	%	Change in HbA1c Mean (95% CI)
Antibody negative	621	32.9%	-0.83 (-0.920, -0.746)
Antibody positive			
<LLOQ	854	45.2%	-0.88 (-0.963, -0.796)
≥ LLOQ to ≤ 100 nmol/L	370	19.6%	-0.64 (-0.751, -0.528)
>100 nmol/L	45	2.4%	-0.16 (-0.418, 0.096)

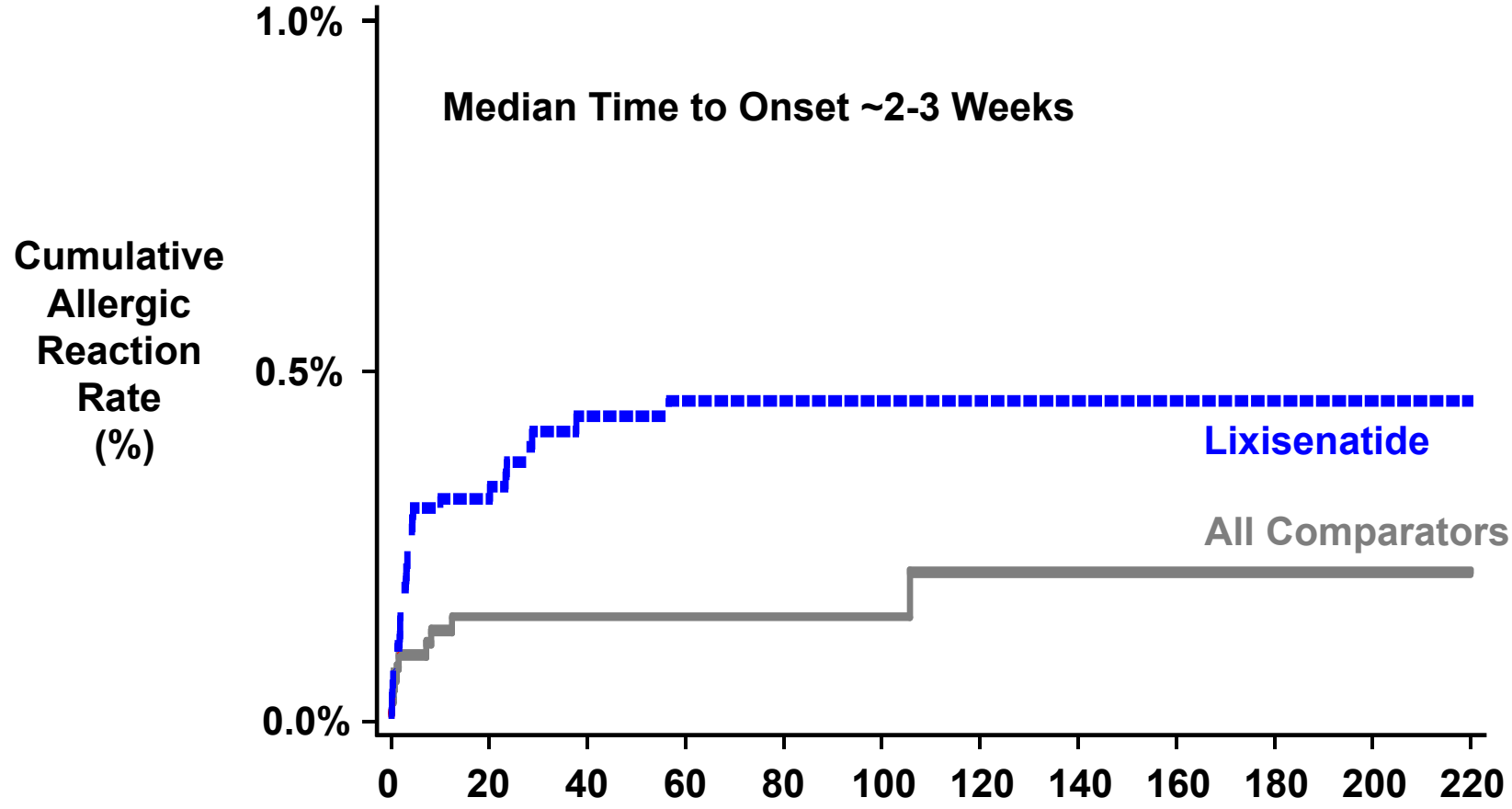


* Includes all patients for which antibody concentration is available regardless of the availability of antibody status
Pooled data of 8 pivotal phase 3 placebo-controlled studies - mITT population
LLOQ: lower limit of quantification; BL: baseline

Drug-Related Allergic Reactions by ADA Status: Lixisenatide Phase 3 Placebo-Controlled Studies

EntireTreatment Period	Lixisenatide Patients	
	n/N (%)	EAIR Per 100 PY
Patients with Drug-Related Allergic Reactions (ARAC)	17/2869 **(0.6%)**	**0.5**
Patients with Evaluable ADA status	2800	
ADA Status		
Positive	11/2032 **(0.5%)**	**0.4**
Negative	4/768 **(0.5%)**	**0.6**

Time to Onset of AEs: Adjudicated as Allergic Reaction Possibly Related to IP by ARAC



Numbers at Risk

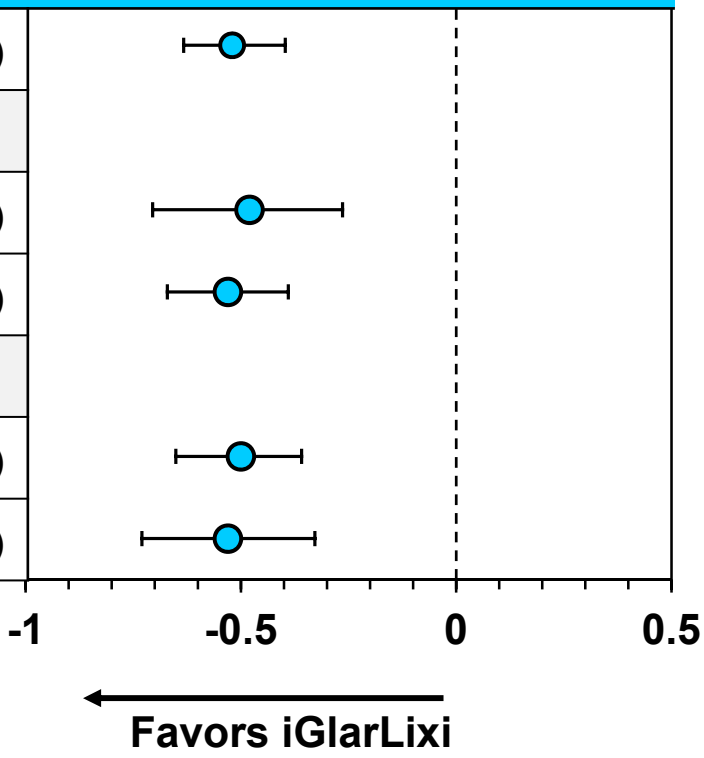
All Comparators	6057	5218	3711	3546	2805	1713	1071	675	361	183	36	1
Lixisenatide	7312	5800	4561	4331	3397	1894	1049	653	365	176	38	3

Study 405 - Change in HbA_{1c} By Baseline Insulin Dose Category

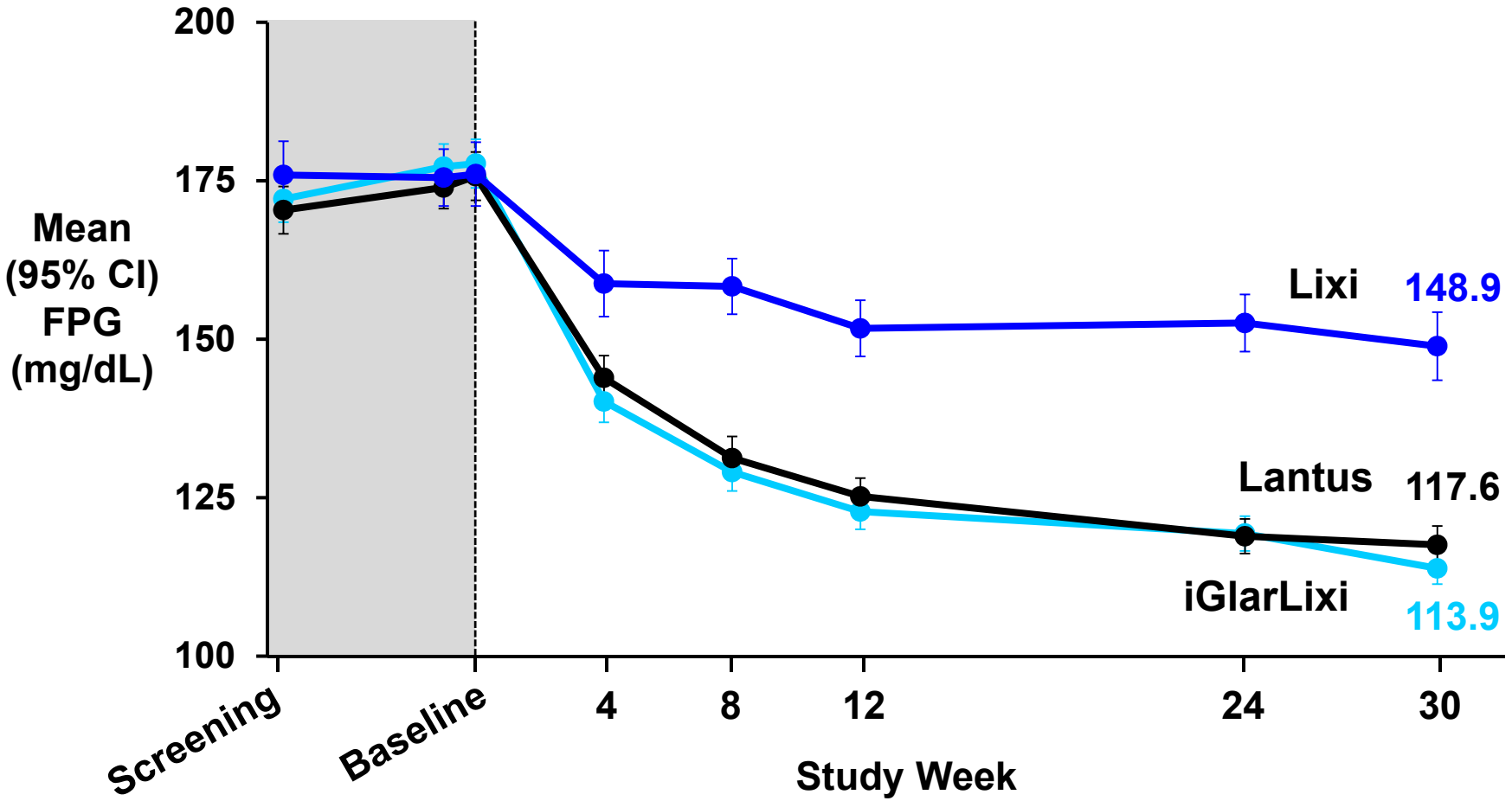
	Study 405 (N=736)					
	iGlarLixi (N=366)			Lantus (N-365)		
	n	Baseline HbA_{1c}	LS Mean change from BL (SE)	n	Baseline HbA_{1c}	LS Mean change from BL (SE)
Overall	364	8.07	-1.13 (0.06)	364	8.08	-0.62 (0.06)
Baseline Insulin dose						
<30	108	8.00	-1.07 (0.09)	101	7.87	-0.59 (0.09)
≥ 30	256	8.10	-1.16 (0.06)	263	8.15	-0.63 (0.06)
<40	240	7.98	-1.18 (0.07)	239	8.04	-0.67 (0.06)
≥ 40	124	8.24	-1.05 (0.08)	125	8.15	-0.52 (0.08)

Study 405 - Change in HbA_{1c} By Baseline Insulin Dose Category

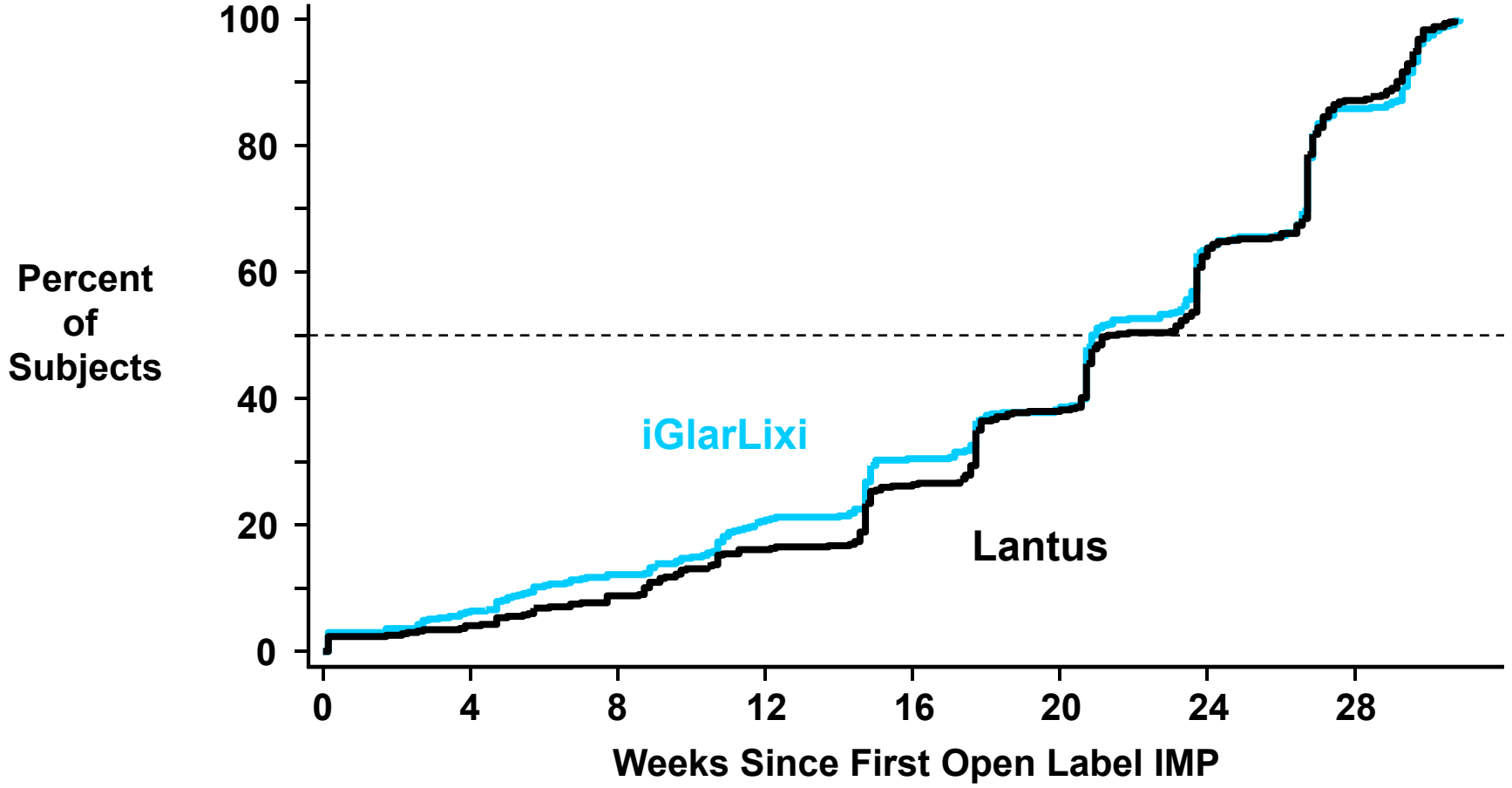
Study 405	iGlarLixi (N)	Lantus (N)	Mean Difference (95% CI)
Overall	364	364	**-0.52** (-0.63, -0.40)
Baseline Insulin dose			
<30	108	101	**-0.48** (-0.71, -0.26)
≥ 30	256	263	**-0.53** (-0.67, -0.39)
<40	240	239	**-0.50** (-0.65, -0.36)
≥ 40	124	125	**-0.53** (-0.73, -0.33)



Trial 404 Mean Fasting Plasma Glucose by Visit



iGlarLixi Study 404: KM Plot Time to Lantus Dose Stabilization - Safety Population



iGlarLixi	469	440	410	369	323	287	170	66
Lantus	467	447	425	391	344	289	175	60

Studies 404 and 405: Number of Patients with Final Insulin Dose of 60 U

	Study 404	
	iGlarLixi (N=468)	Lantus (N=466)
Number of Patients receiving Final Insulin Dose of 60U (N)	73/468 (15.6%)	94/466 (20.2%)

	Study 405	
	iGlarLixi (N=366)	Lantus (N=365)
Number of Patients receiving Final Insulin Dose of 60U (N)	99/366 (27.0%)	112/365 (30.7%)

mITT population

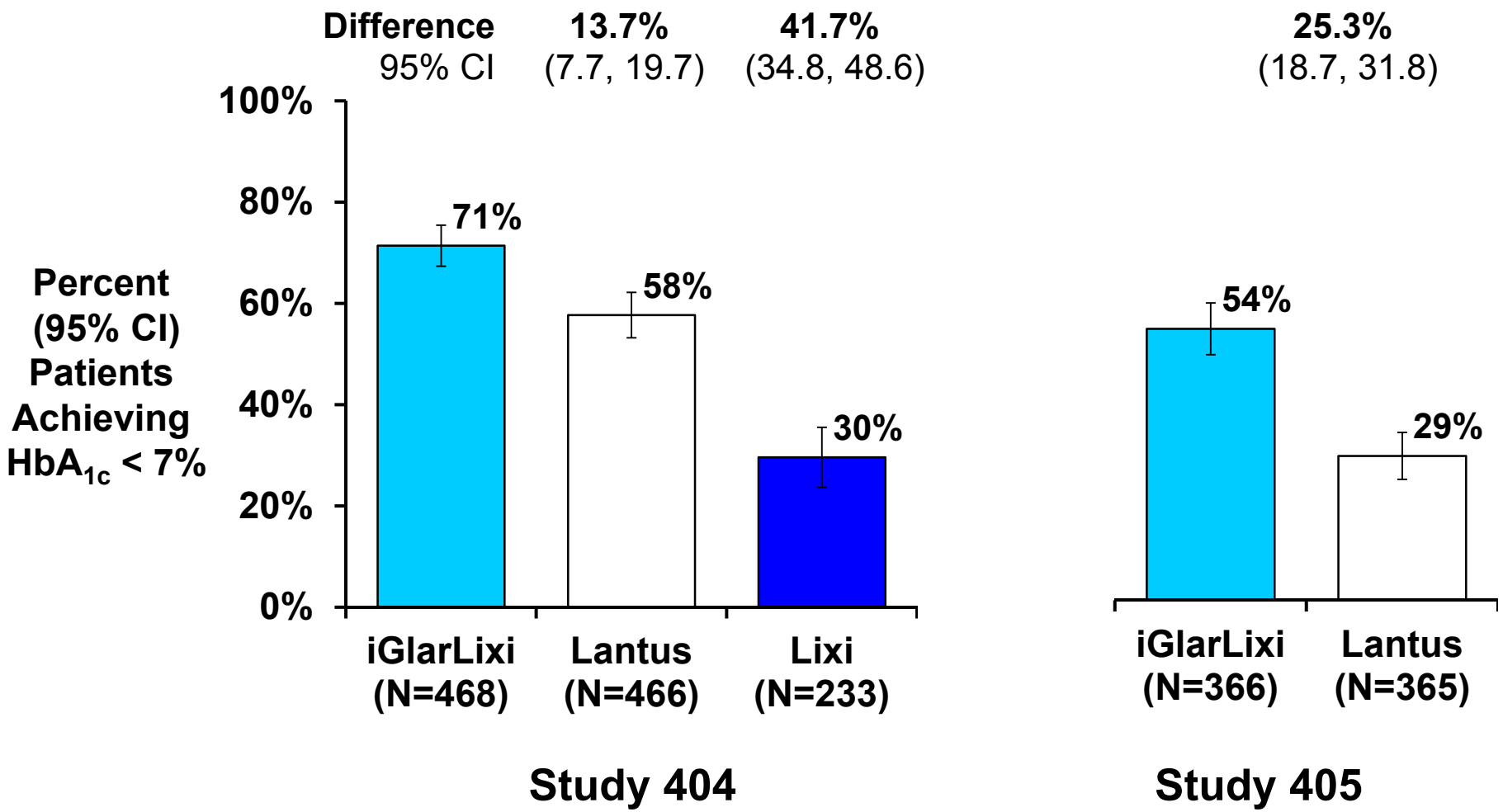
Percentage of Patients with Final Insulin Dose of 60 Units and HbA1c < 7.0% at Week 30

mITT Population	STUDY 404		STUDY 405	
	iGlarLixi N=468	Lantus N=466	iGlarLixi N=366	Lantus N=365
Final Insulin Dose = 60U	73	94	99	112
Final Insulin Dose = 60 U and HbA1c <7%	39 (53%)	48 (51%)	43 (43%)	27 (24%)

iGlarLixi: Nausea Events by Severity

	Pooled Phase 3		Study 404
	iGlarLixi (N=834)	Lantus (N=832)	Lixisenatide (N=233)
Nausea	10.0%	2.3%	24%
Mild	6.5%	1.8%	15.5%
Moderate	3.4%	0.5%	6.9%
Severe	0.1%	0	1.7%

iGlarLixi: Proportion of Patients who Completed Treatment with HbA_{1c} <7.0% at Week 30



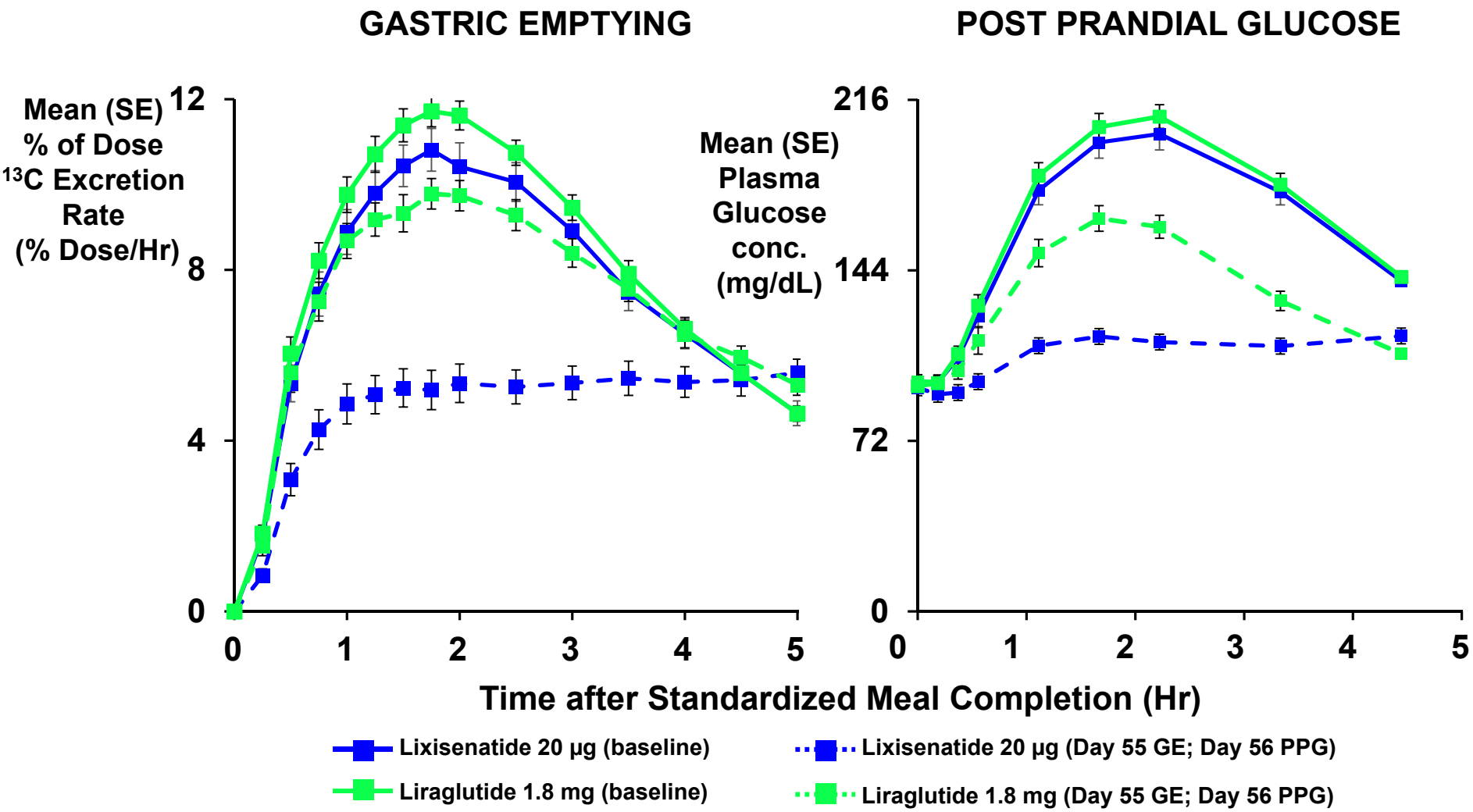
Patients who discontinued treatment or were Rescued are Non-responders

Lixisenatide QD vs. Exenatide BID

	Lixisenatide QD (N=315)	Exenatide BID (N=315)
HbA_{1c} (%)		
Mean baseline (SD)	7.97 (0.82)	7.96 (0.77)
LS Mean change from baseline (SE)	-0.79 (0.053)	-0.96 (0.054)
LS Mean Diff (SE) vs Exenatide	0.17 (0.067)	
[95%CI]	[0.033 to 0.297]	
HbA_{1c} <7%	48.5%	49.8%

mITT population, 24-week data, 0.4% non-inferiority margin

Lixisenatide Slows Gastric Emptying and Suppresses PPG Excursions



Patients with T2D, Repeated 20 µg daily dose, PDY12625

Proposed Educational Activities

Clinicians

- US Prescribing Information
- Dosing Guide & product training materials
- Product Website
- Customer Service Line

Pharmacists

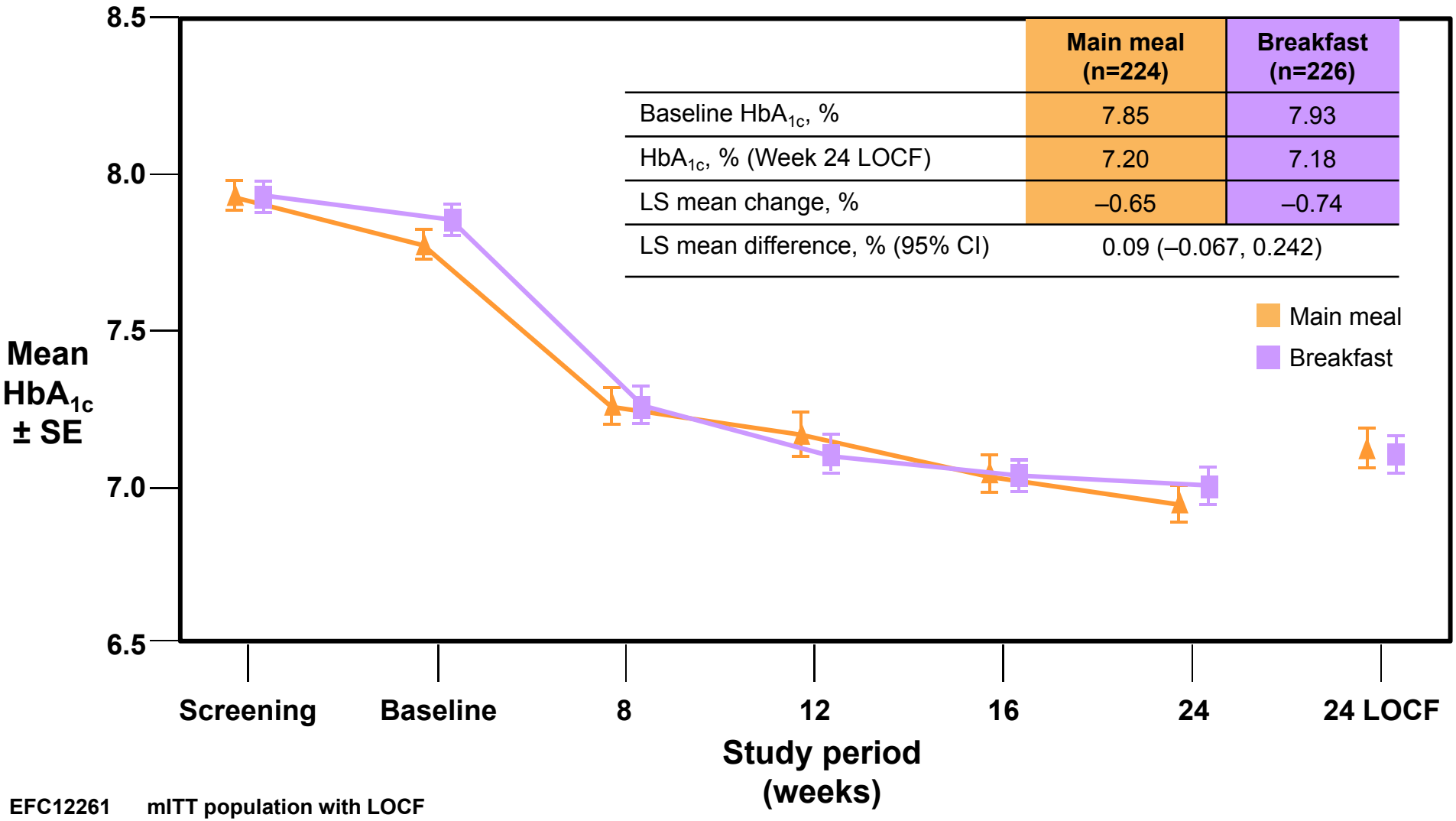
- US Prescribing Information/IFU
- Dosing Guide & educational materials
- Product website
- Digital campaign to pharmacists (with dosing information)
- Customer service Line

Patients

- Instructions for Use (IFU)
- Medication Guide
- Starter kits
- Injection training video
- Product website
- Patient support Program (COACH)
- Customer Service Line

Primary Endpoint: HbA_{1c} Change Over Time: Main Meal Study

	Main meal (n=224)	Breakfast (n=226)
Baseline HbA_{1c}, %	7.85	7.93
HbA_{1c}, % (Week 24 LOCF)	7.20	7.18
LS mean change, %	–0.65	–0.74
LS mean difference, % (95% CI)	0.09 (–0.067, 0.242)	

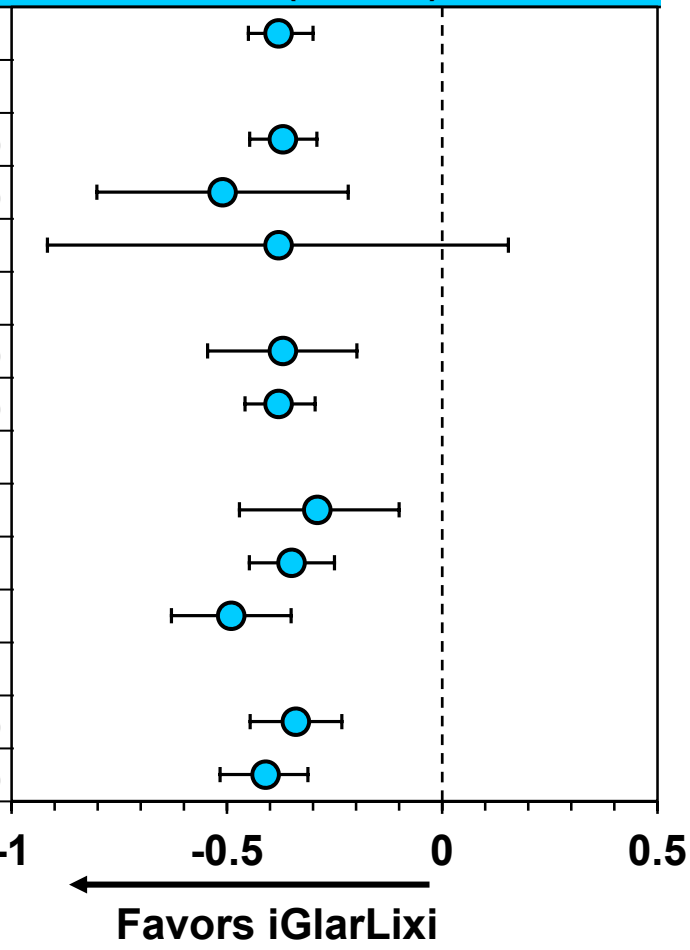


EFC12261 mITT population with LOCF

CI, confidence interval; LS, least squares; LOCF, last observation carried forward;SE, standard error

Difference in HbA_{1c} Reductions Between iGlarLixi and Lantus Consistent Across Subgroups (1)

Pooled Data Study 404 and 405	iGlarLixi (N)	Lantus (N)	LS Mean Difference (95% CI)
Overall	834	831	**-0.38** (-0.45, -0.30)
Race			
Caucasian	750	751	**-0.37** (-0.45, -0.29)
Black	50	54	**-0.51** (-0.80, -0.22)
Asian/Oriental	20	15	**-0.38** (-0.92, 0.15)
Ethnicity			
Hispanic	149	151	**-0.37** (-0.55, -0.20)
Non Hispanic	682	677	**-0.38** (-0.46, -0.30)
Age			
<50	135	122	**-0.29** (-0.47, -0.10)
≥ 50 to <65	454	474	**-0.35** (-0.45, -0.25)
≥ 65	242	232	**-0.49** (-0.63, -0.35)
Gender			
Male	386	410	**-0.34** (-0.45, -0.23)
Female	445	418	**-0.41** (-0.52, -0.31)



iGlarLixi: Subgroup Analyses of TEAEs by Race in Phase 3 Study Pool