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# LX4211, a Dual Inhibitor of SGLT2 and SGLT1, Shows Rapid and Significant Improvement in Glycemic Control Over 4 Weeks in Patients with Type 2 Diabetes Mellitus

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# Disclosure Statement

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# Forward-looking Statements

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This presentation contains “forward-looking statements,” including statements relating to the characterization of the safety and efficacy profile of LX4211 observed in the Phase 2 clinical trial as positive or favorable, the characterization of the results of the Phase 2 clinical trial of LX4211 as demonstrating the potential for a therapeutic benefit for patients with type 2 diabetes, the mechanism of action of LX4211, and the potential therapeutic and commercial potential of LX4211 generally. Results reported as trends were not statistically significant. This presentation also contains forward-looking statements relating to Lexicon’s growth and future operating results, discovery and development of products, strategic alliances and intellectual property, as well as other matters that are not historical facts or information. All forward-looking statements are based on management’s current assumptions and expectations and involve risks, uncertainties and other important factors, specifically including those relating to Lexicon’s ability to successfully conduct clinical development of LX4211 and preclinical and clinical development of its other potential drug candidates, advance additional candidates into preclinical and clinical development, obtain necessary regulatory approvals, achieve its operational objectives, obtain patent protection for its discoveries and establish strategic alliances, as well as additional factors relating to manufacturing, intellectual property rights, and the therapeutic or commercial value of its drug candidates, that may cause Lexicon’s actual results to be materially different from any future results expressed or implied by such forward-looking statements. Information identifying such important factors is contained under “Factors Affecting Forward-Looking Statements” and “Risk Factors” in Lexicon’s annual report on Form 10-K for the year ended December 31, 2009, as filed with the Securities and Exchange Commission. Lexicon undertakes no obligation to update or revise any such forward-looking statements, whether as a result of new information, future events or otherwise.

# Introduction

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- ❖ Type 2 Diabetes Mellitus (T2DM) is a chronic, progressive disease
  - Increases risk for renal failure, blindness, MI and stroke
  - >242 million people worldwide have T2DM\*
- ❖ Available therapies often limited by:
  - Side effects
  - Insufficient efficacy
  - Undesirable route of administration
- ❖ SGLT inhibitors are an emerging class of agents that block renal glucose reabsorption, resulting in:
  - Improved glucose homeostasis that is not insulin-dependent
  - Gradual urinary glucose loss that minimizes hypoglycemia risk
- ❖ Metabolic advantages:
  - Lower blood pressure
  - Weight loss

\**Diabetes Atlas* 3<sup>rd</sup> edition (International Diabetes Federation, Brussels, Belgium, 2006)

# LX4211 Is a Potent Inhibitor of SGLT2 and SGLT1

- SGLT2 is the transporter responsible for the majority of glucose reabsorption by the kidney
- SGLT1 is the transporter responsible for the majority of glucose absorption by the small intestine

	LX4211	Dapagliflozin *	Canagliflozin *	BI-10773 *
Human SGLT2 IC50 ( $\mu\text{M}$ )	0.0018	0.0011	0.0022	0.0031
Human SGLT1 IC50 ( $\mu\text{M}$ )	0.0363	1.32	0.44	> 7.75
SGLT2/SGLT1 Selectivity	20X	1200X	200X	> 2500X

\* Data are from Washburn WN, *Expert Opin Ther Pat* 19:1485–1499, 2009

# LX4211 Phase 2a Study

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## Design:

Phase 2a, single-center, randomized, double-blind, placebo controlled, multiple-dose study in subjects with T2DM

## Objectives:

- Evaluate safety, tolerability and pharmacokinetics of orally administered LX4211
- Evaluate efficacy of LX4211 over 28 days by assessing:
  - Urinary glucose excretion
  - Fasting plasma glucose and insulin levels
  - Response to oral glucose tolerance testing
  - Plasma fructosamine levels
  - Hb<sub>A1c</sub> Levels
  - Postprandial glucose levels
  - CV and metabolic parameters

# LX4211 Phase 2a Study

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## Methods:

- Subjects randomized to treatment in a 1:1:1 ratio (N=36)
  - LX4211, 150 mg/day as a single oral dose
  - LX4211, 300 mg/day as a single oral dose
  - placebo
- Screening period included a 14-day washout of metformin
- Sequestered from Day -5 through the 28-day dosing period
- Received a standard low glycemic index diet based on baseline BMI
  - BMI < 35kg/m<sup>2</sup>: 2500 calories
  - BMI ≥ 35kg/m<sup>2</sup>: 2800 calories

# LX4211 Phase 2a Study

## Baseline Characteristics:

	150mg	300mg	PBO
Median Age	53	55	55
Male/Female	6/6	8/4	6/6
Weight (kg)	86.06	98.67	81.65
Fasting Plasma Glucose (mg/dL)	175.3	188.2	192.4
Urine Glucose (g/day)	16.6	13.8	16.6
Systolic BP (mm Hg) – seated	123.8	121.3	117.7
Diastolic BP (mm Hg) – seated	79.5	77.0	77.0

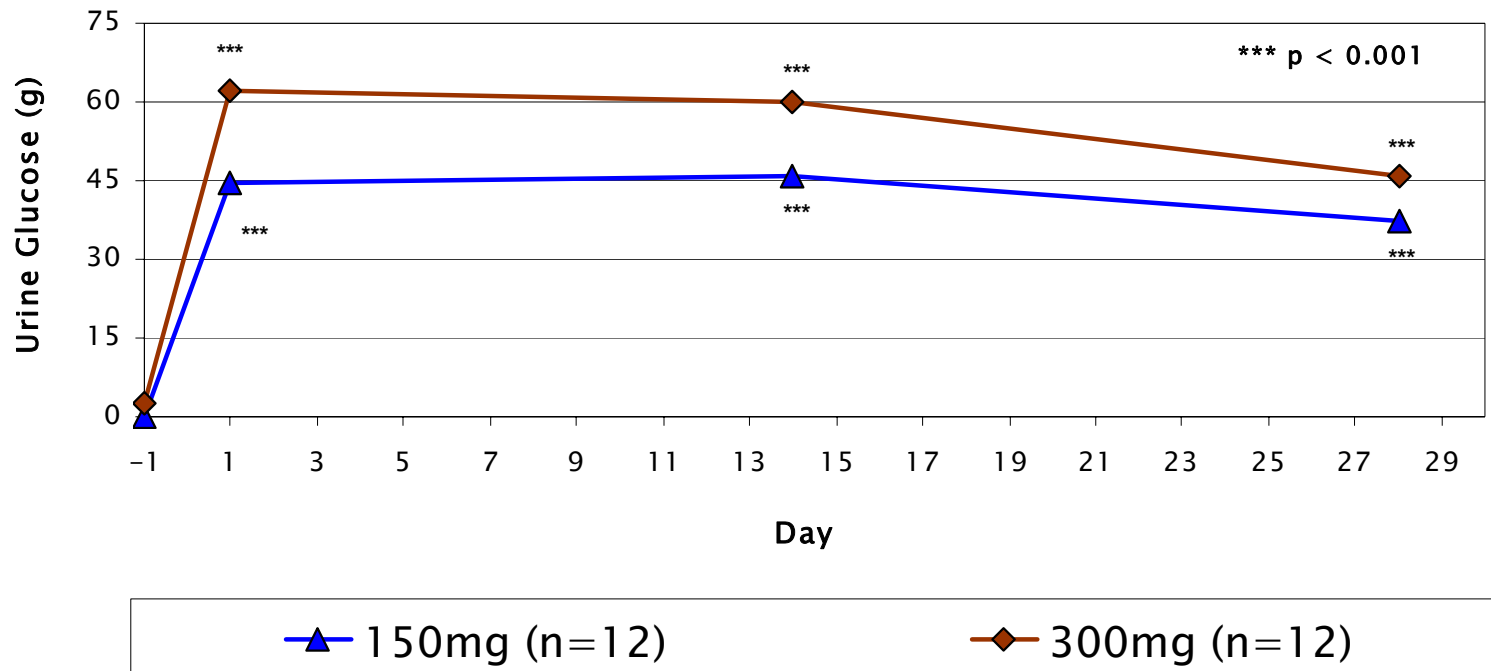
# Adverse Events

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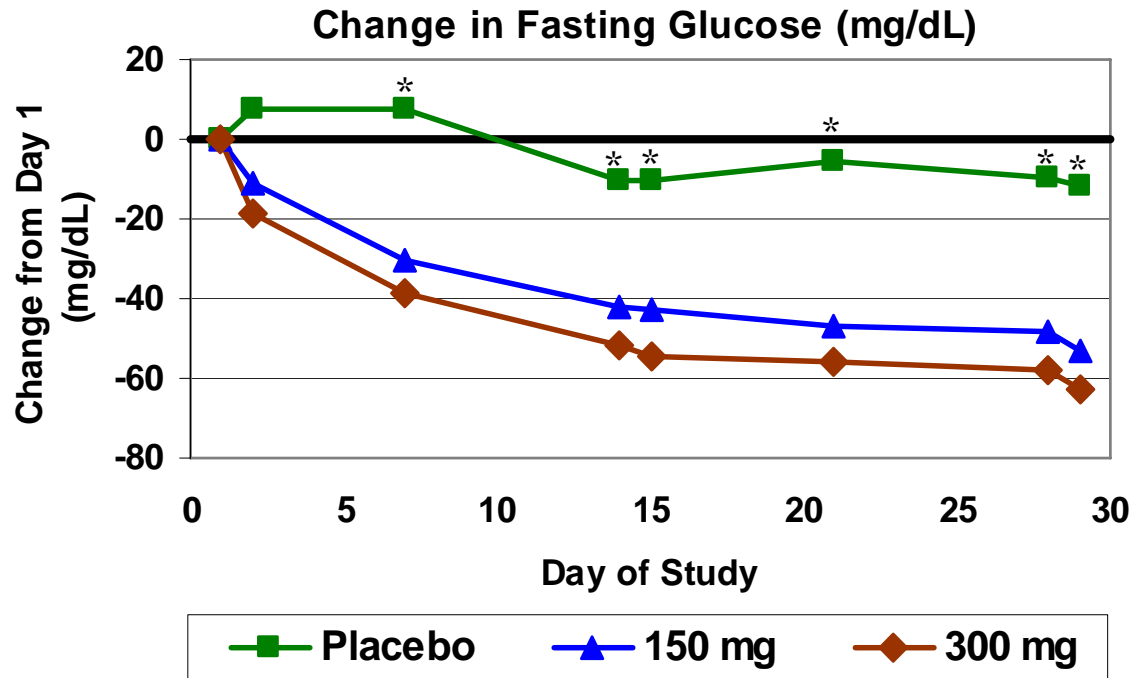
- No serious AEs, deaths, or discontinuation due to AEs
- No trends of clinical concern
- Treatment-emergent AEs were generally mild and equally distributed across all dose groups, including placebo
- No treatment-emergent genital infections or UTIs observed

# Subjects Receiving LX4211 Exhibited Enhanced Urinary Glucose Excretion

Mean 24-Hour Urine Glucose Excretion – Placebo Adjusted



# Fasting Plasma Glucose (FPG) Was Improved Over 28 Days of Dosing With LX4211

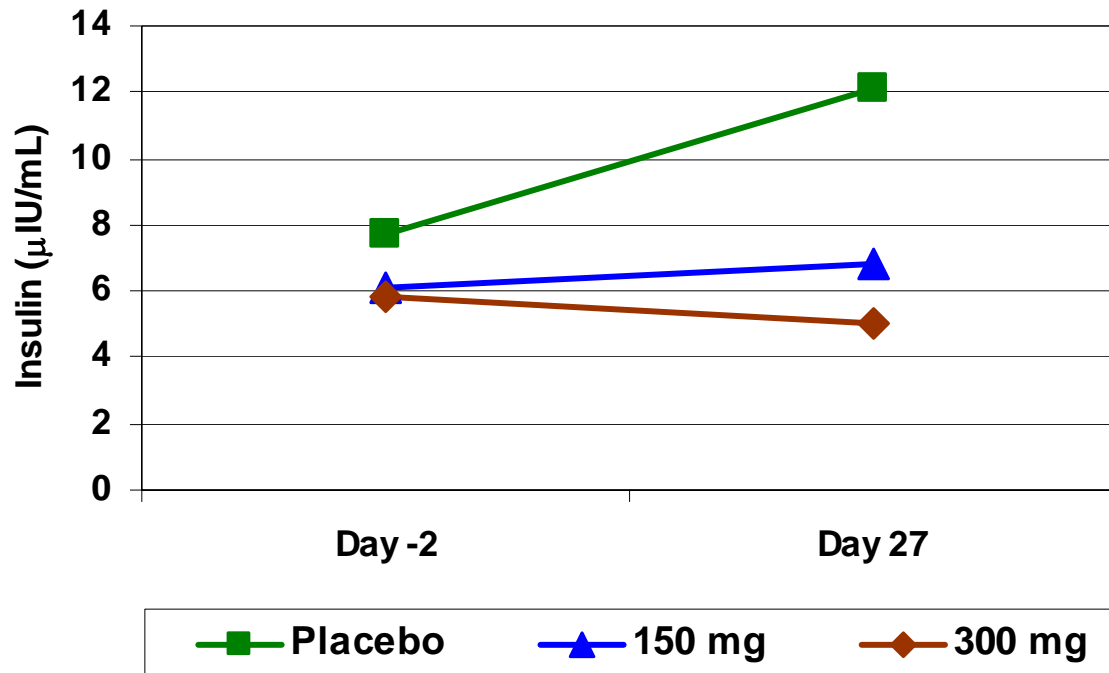


\*  $p < 0.01$  vs 150 mg and 300 mg groups

- 50% of subjects dosed with LX4211 achieved a FPG  $< 120$  mg/dl, compared to 0% in the placebo group ( $p = 0.006$ )
- 33.3% achieved a FPG  $< 105$  mg/dl, compared to 0% in the placebo group ( $p = 0.037$ )

# Fasting Insulin Concentrations were Lower After 27 Days of Treatment with LX4211

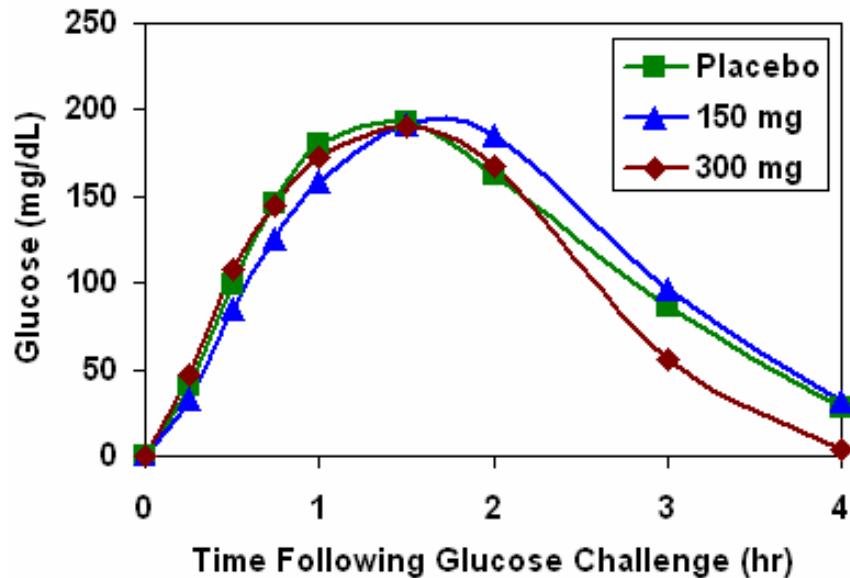
Effect of LX4211 on Fasting Insulin ( $\mu\text{IU/mL}$ )



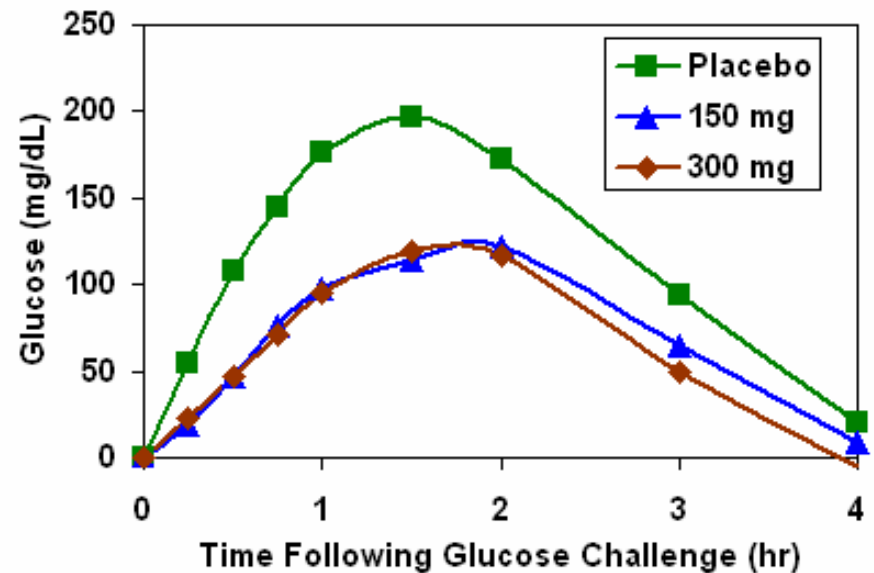
# LX4211 Treatment Resulted in Decreased Glucose Excursions During Oral Glucose Tolerance Testing

## Blood Glucose Above Fasting

Day -2



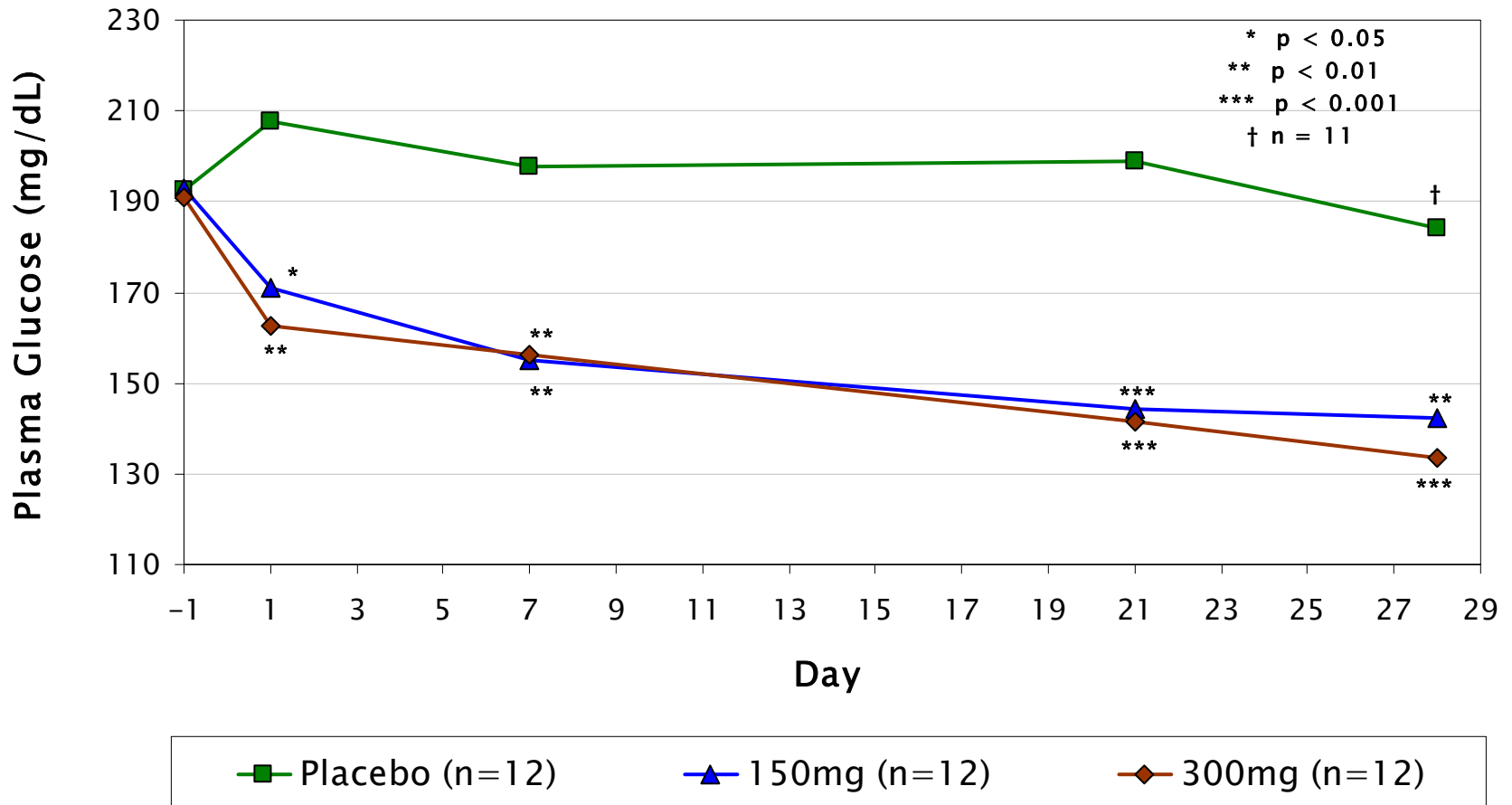
Day 27



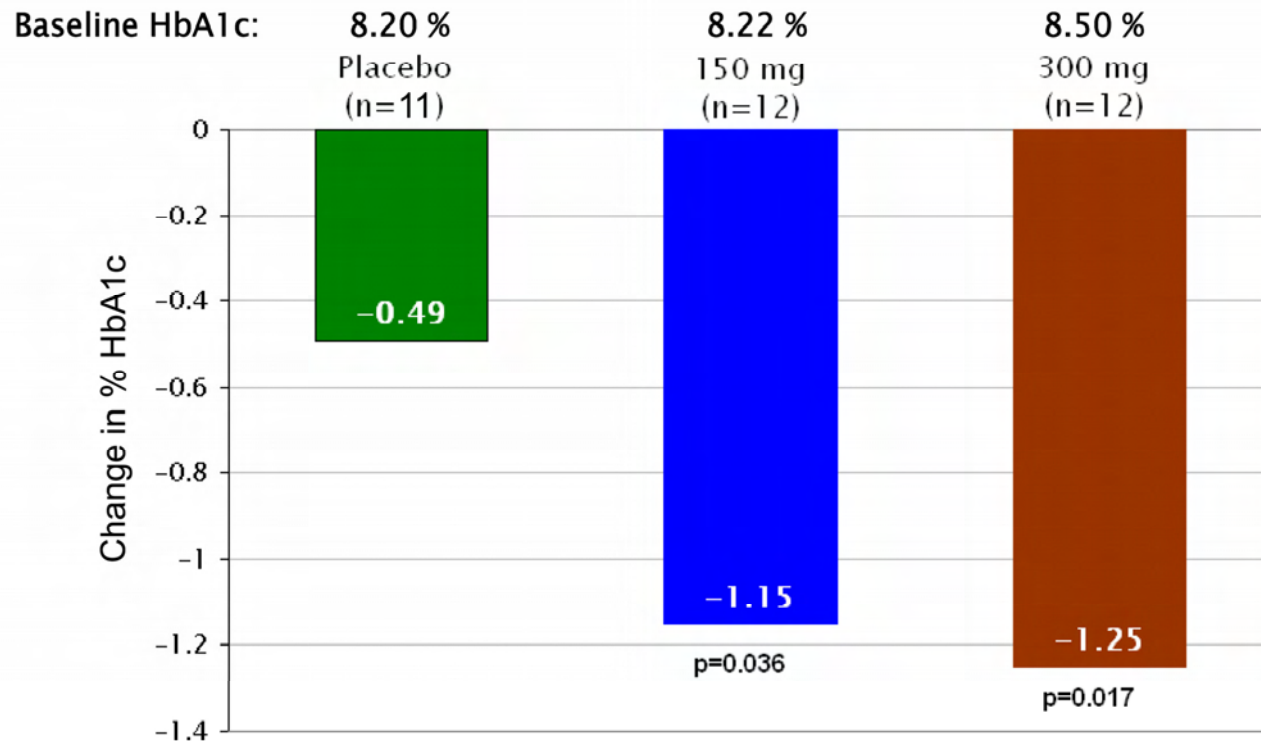
$p < 0.001$ , placebo AUC vs  
AUC of 150 mg or 300 mg

# Subjects Dosed With LX4211 Exhibited Improved 2-hour Postprandial Glucose Levels

## Mean Post-Prandial Glucose



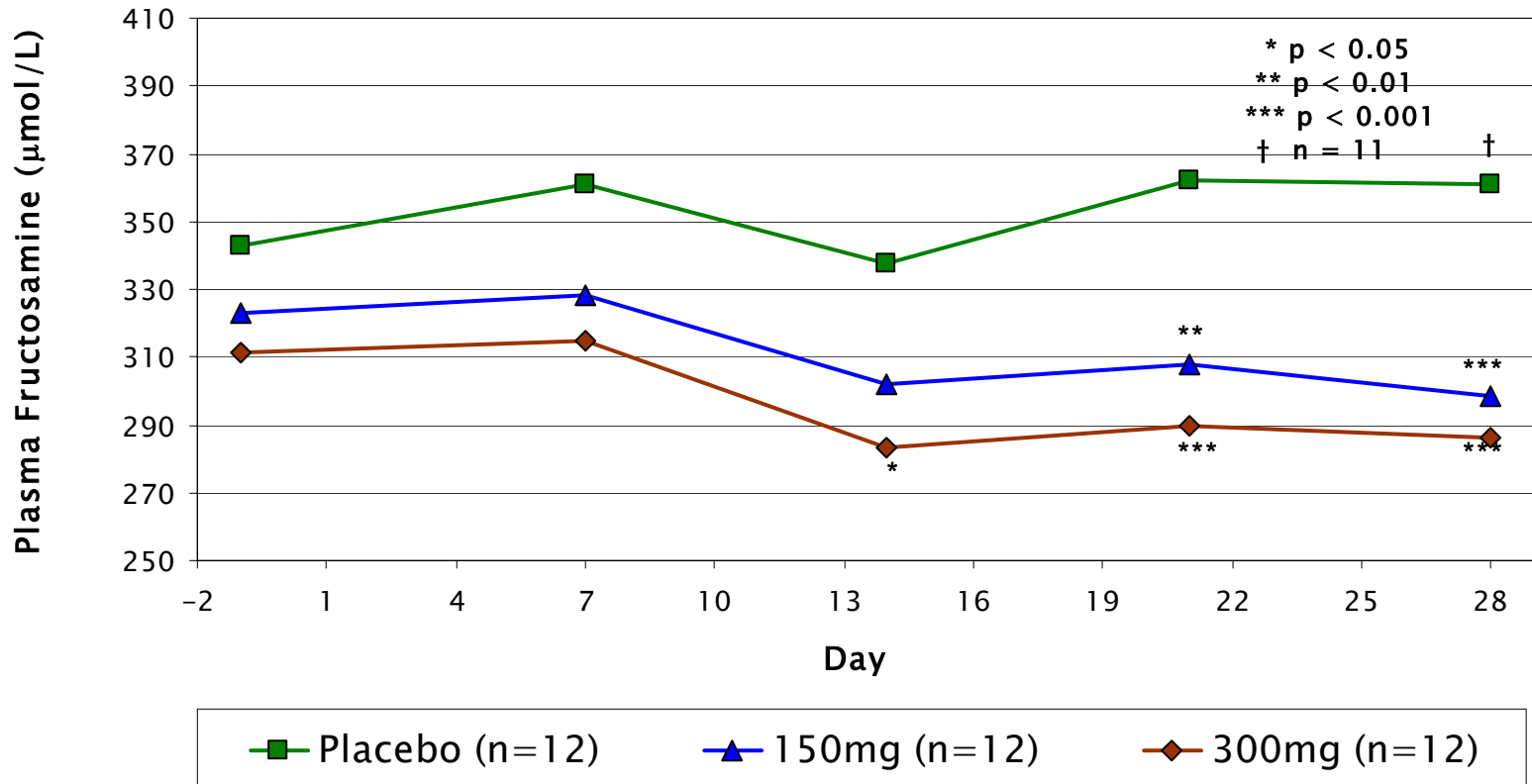
# Hemoglobin A1c (HbA1c) Levels Decreased After Only Four Weeks of Treatment with LX4211



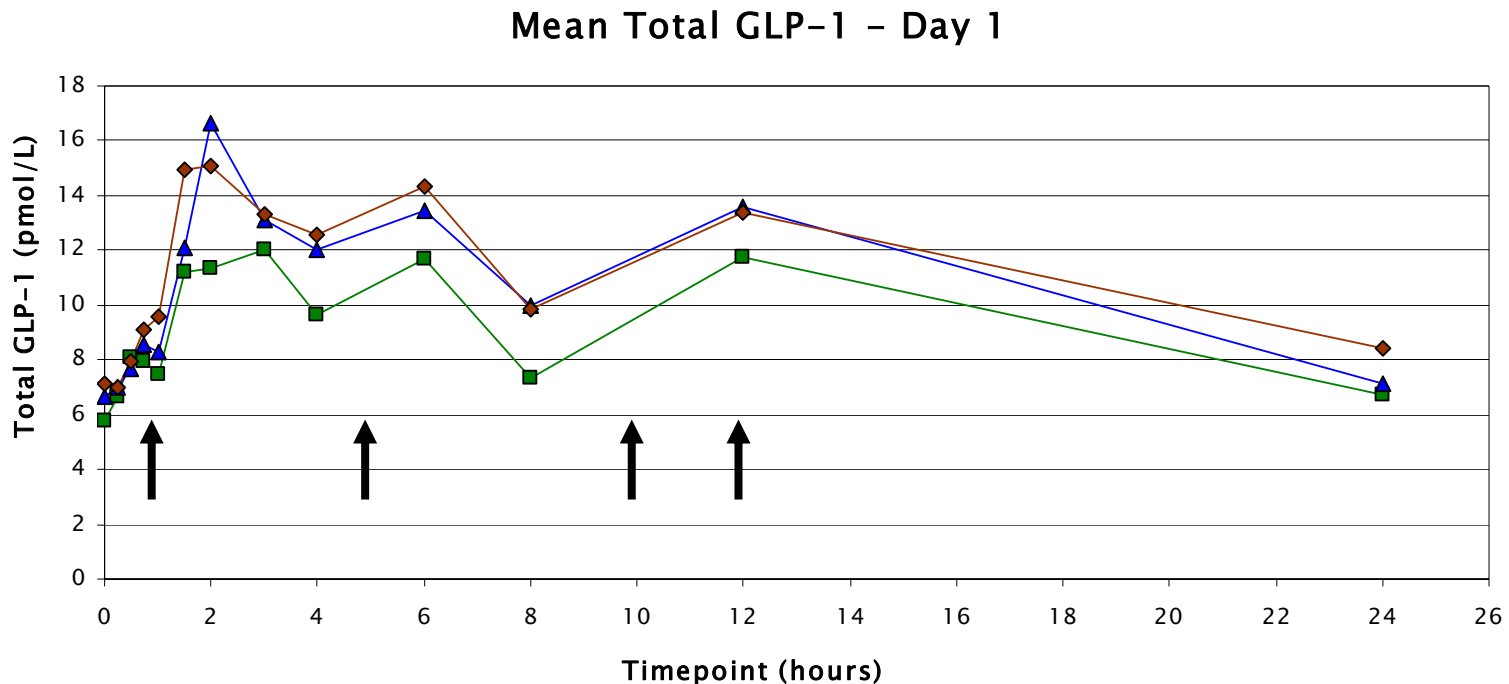
- Absolute change (relative to placebo) was 0.66 for the 150 mg dose group and 0.76 for the 300 mg dose group

# Plasma Fructosamine Levels Were Significantly Lower With LX4211 Treatment

Mean Plasma Fructosamine



# LX4211 Treatment on Day One Showed a Trend of Greater Increases in Total GLP-1 Levels With Meals



(Arrows identify mealtimes; dose at time 0)

■ Placebo (n=12)

▲ 150mg (n=12)

◆ 300mg (n=12)

Similar results observed on Day 28

# Summary and Conclusions

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- In subjects with T2DM participating in the Phase 2a Study, LX4211 treatment:
  - was well-tolerated with a favorable safety profile
  - rapidly and significantly improved glycemic parameters:
    - fasting plasma glucose and insulin
    - oral glucose tolerance
    - postprandial plasma glucose
    - HbA1c and plasma fructosamine
  - showed a trend of increased serum total GLP-1 with meals
- LX4211 may be a safe and effective way to reduce hyperglycemia-associated complications of T2DM. Further evaluation of LX4211 in this population is warranted.
- Dual SGLT2/SGLT1 inhibition may provide enhanced glycemic control over SGLT2 inhibition alone.