# DIABETES UPDATE CALL

October 4, 2018

Lilly

# AGENDA

## OPENING REMARKS

**Enrique Conterno**, Senior Vice President, President Lilly Diabetes and Lilly USA

## INTRODUCTION OF LY3298176

**Ruth Gimeno,** Vice President Diabetes and Metabolic Research

## LY3298176 PHASE 2 DATA AND PHASE 3 DEVELOPMENT PLAN

**Brad Woodward**, Incretins Platform Team Leader

## QUESTION AND ANSWER SESSION

# SAFE HARBOR PROVISION

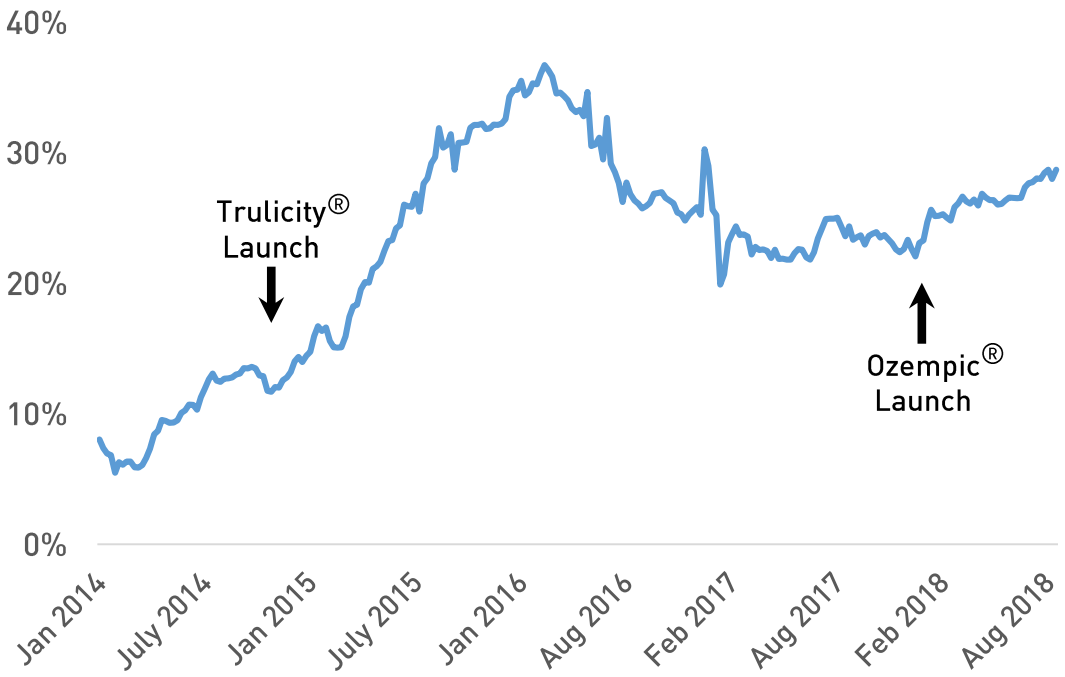
This presentation contains forward-looking statements that are based on management's current expectations, but actual results may differ materially due to various factors. The company's results may be affected by factors including, but not limited to, the risks and uncertainties in pharmaceutical research and development; competitive developments; regulatory actions; litigation and investigations; business development transactions; economic conditions; and changes in laws and regulations, including health care reform.

For additional information about the factors that affect the company's business, please see the company's latest Forms 10-K and 10-Q filed with the Securities and Exchange Commission.

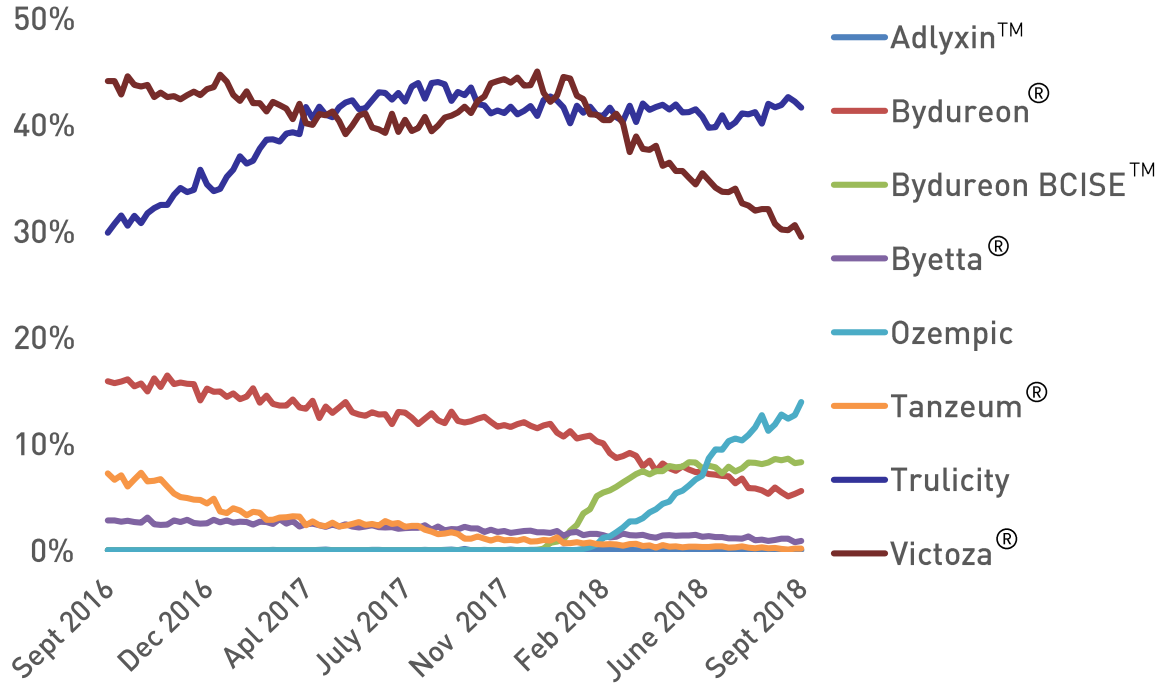
**The company undertakes no duty to update forward-looking statements.**

# U.S. GLP-1 MARKET GROWTH EXPECTED TO CONTINUE

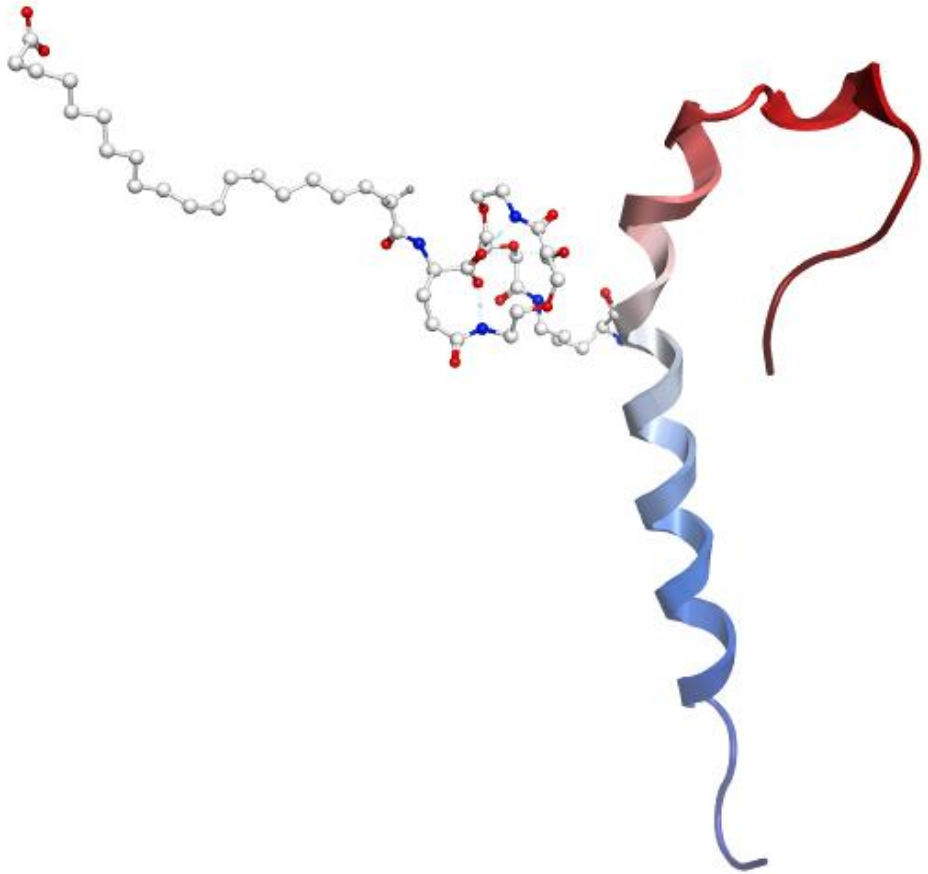
## U.S. GLP-1 Market Growth
*(4 week TRx YoY % Growth)*




## U.S. New Therapy Starts SOM



# THE MOLECULE



Molecular Weight: 4.8 kDa

## LY3298176

39 amino acid linear peptide conjugated to a C20 fatty diacid moiety via a linker connected to the lysine residue at position 20

Native GIP peptide sequence; modified to bind and activate both the GIP and GLP-1 receptors

Equipotent to native GIP and less potent than native GLP-1

Once-weekly subcutaneous injection dosing



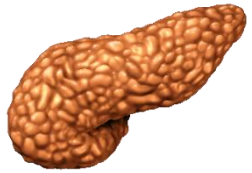
Coskun, T. et al. *Molecular Metabolism.* 2018.

# COMBINING GIP & GLP-1 → NEW PHARMACOLOGY

GLP-1

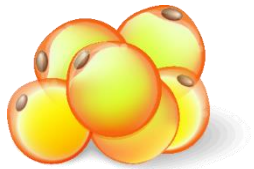
## Proposed Direct Effects

- ↑ Insulin Secretion
- ↓ Glucagon Secretion
- ↓ Food Intake
- ❑ Delayed Gastric Emptying

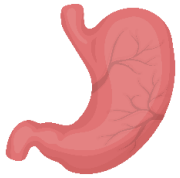


- ↑ Insulin Secretion
- ↑ Glucagon Secretion

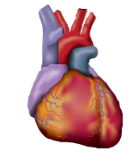
- ↑ Energy Expenditure?
- ↓ Food Intake?



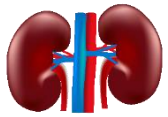
- ↑ Glucose Uptake
- ❑ Altered Lipid Metabolism



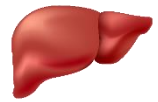
## Proposed Indirect Effects



- ❑ CV Protection?



- ❑ Improved Renal Function?
- ❑ Improved NASH?



- ↑ Insulin Sensitivity

- ↓ Plasma triglycerides

GIP

# PUBLICATIONS

## THE LANCET

**Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial**

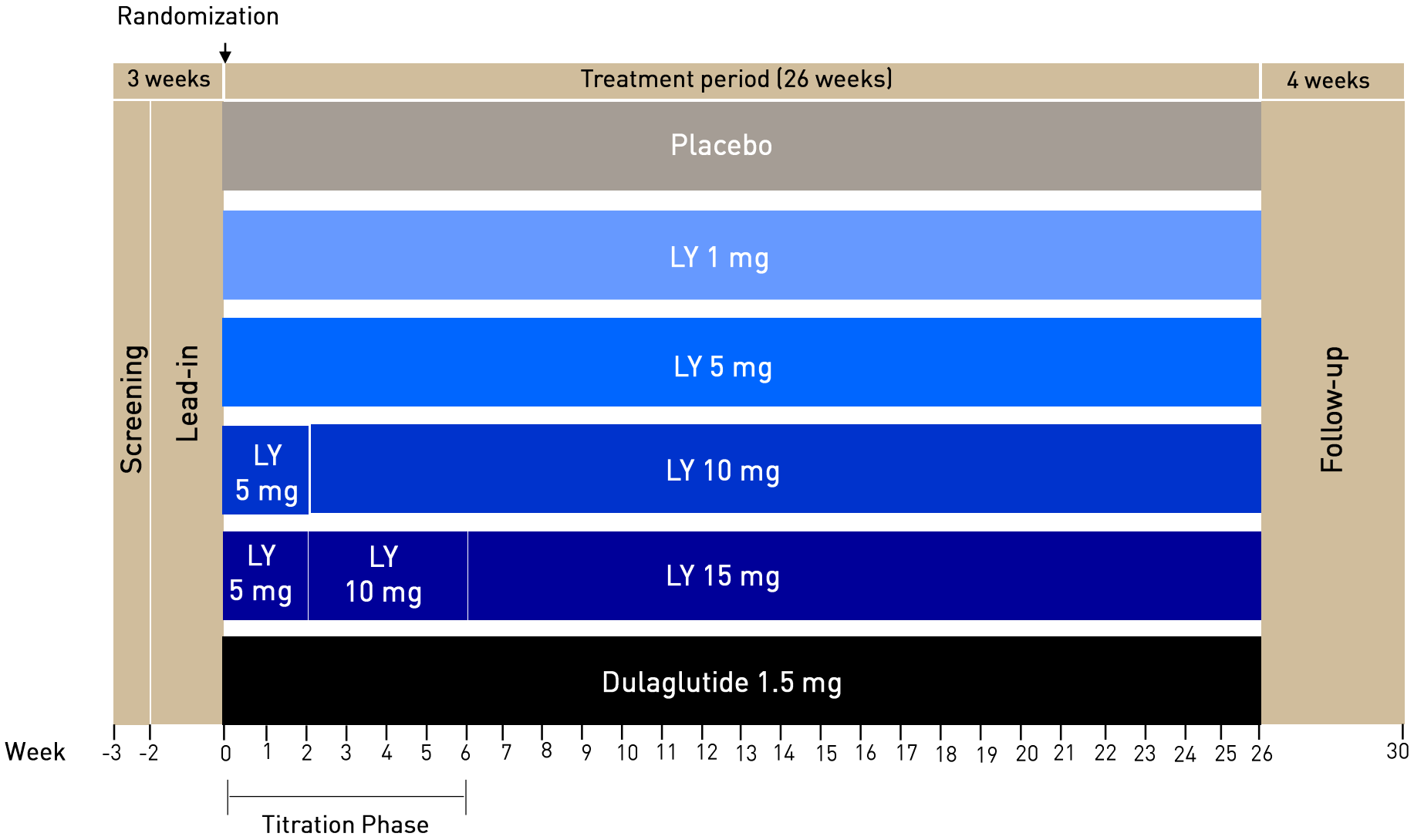
*Juan Pablo Frias, Michael A Nauck, Joanna Van, Mark E Kutner, Xuewei Cui, Charles Benson, Shweta Urva, Ruth E Gimeno, Zvonko Milicevic, Deborah Robins, Axel Haupt*

## MOLECULAR METABOLISM

**LY3298176, A Novel Dual GIP And GLP-1 Receptor Agonist For The Treatment Of Type 2 Diabetes Mellitus: From Discovery To Clinical Proof Of Concept**

Tamer Coskun MD, PhD [1], Kyle W. Sloop PhD [1], Corina Loghin MD [1], Jorge Alsina-Fernandez PhD [1], Shweta Urva PhD [1], Krister B. Bokvist PhD [1], Xuewei Cui PhD [1], Daniel A. Briere MA [1], Over Cabrera PhD [1], William C. Roell PhD [1], Uma Kuchibhotla PhD [1], Julie S. Moyers PhD [1], Charles T. Benson MD [1], Ruth E. Gimeno PhD [1], David A. D'Alessio MD [2], Axel Haupt MD [1]

# LY3298176 PHASE 2B 6-MONTH STUDY DESIGN




**Study objectives:**

- Change in HbA1c At 26 weeks
- Change in body weight at 26 weeks
- Safety and tolerability

**Inclusion criteria:**

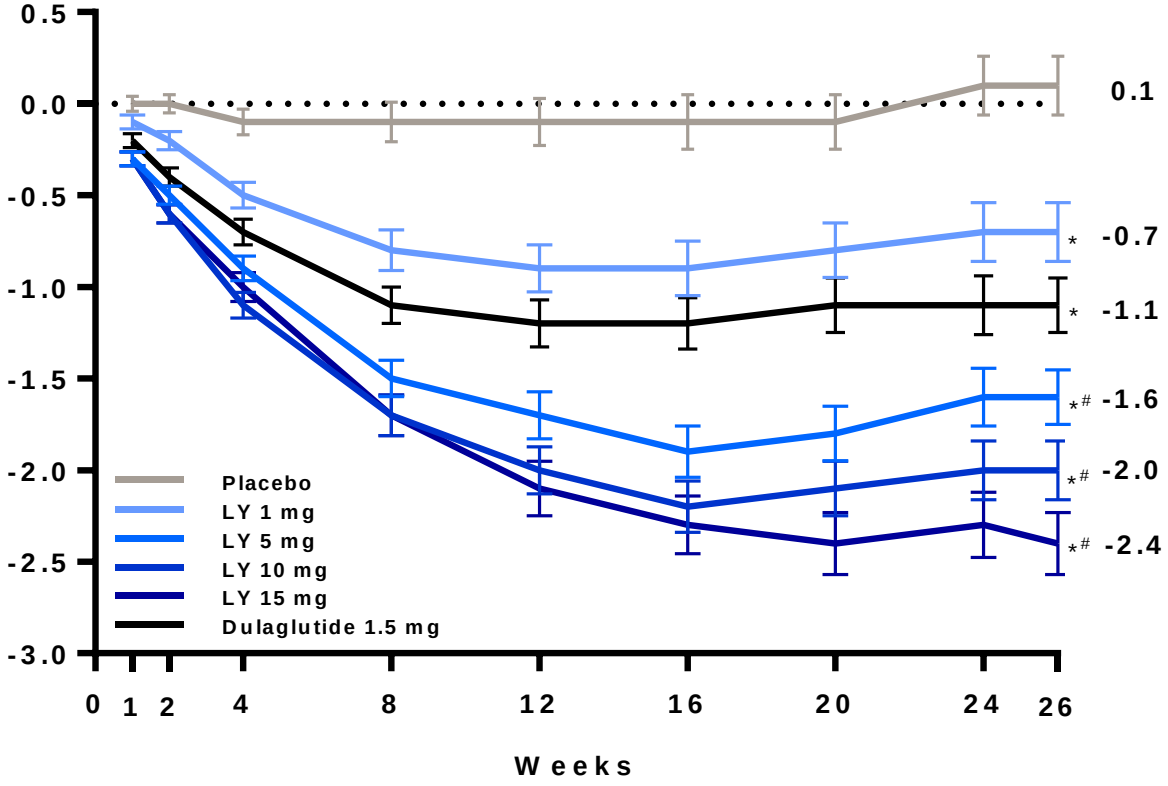
- T2DM
- HbA1c ≥7% to ≤10.5%
- Diet and exercise alone or on a stable dose of metformin



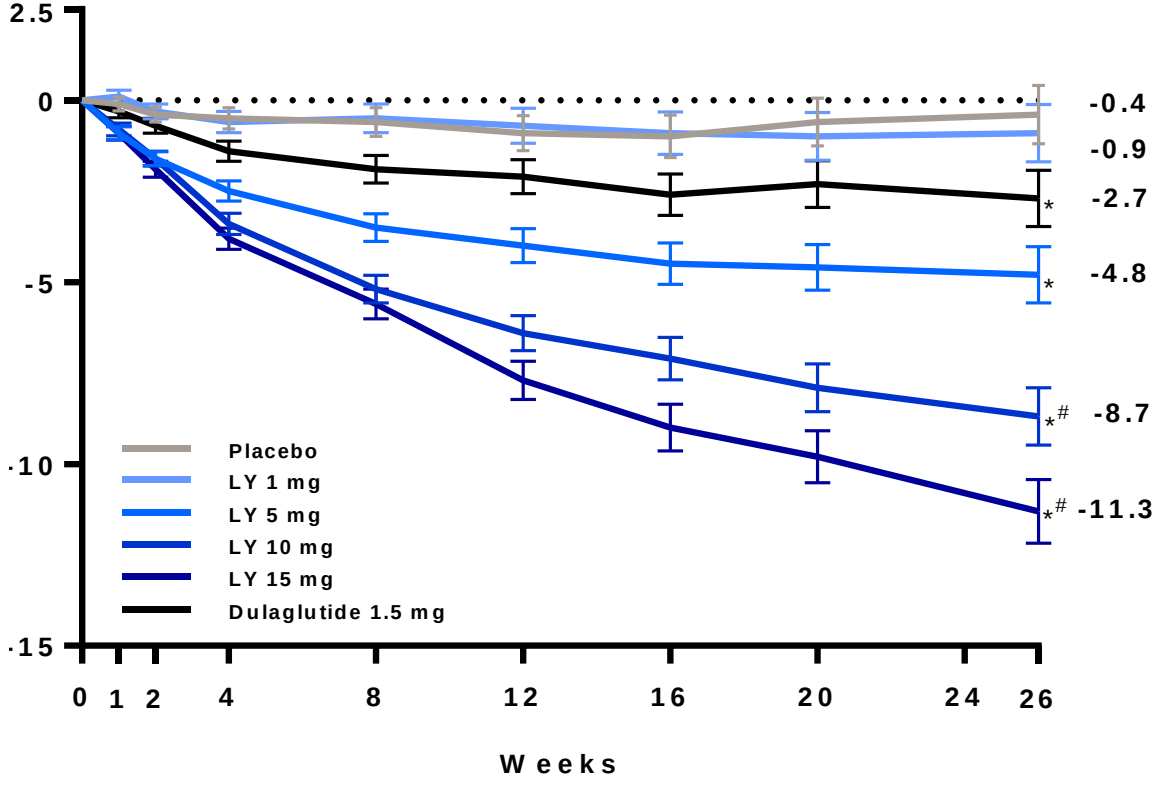
Frias JP et al. *The Lancet.* 2018.

# A1C & WEIGHT REDUCTIONS

## HbA1c (%)




## Weight Loss (Kg)




Data presented are LS mean ± SE. MMRM on treatment analysis. *,#p<.05 vs placebo and vs. dulaglutide 1.5 mg, respectively.

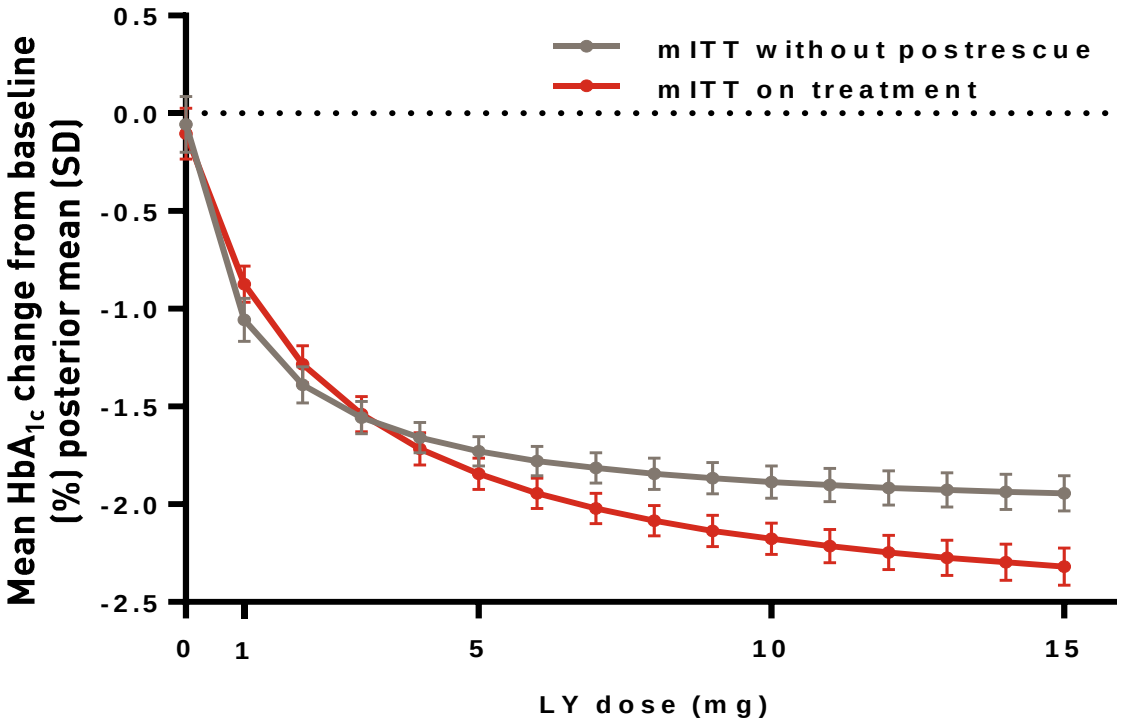
Trial Description: 26 week randomized trial; 1mg, 5mg, 10mg: 2 week titration, 15mg: 6 week titration, dulaglutide 1.5mg
Baseline Characteristics: Mean age 57, weight 91.5 kg, BMI 32.6, A1c 8.1%, 90% on metformin



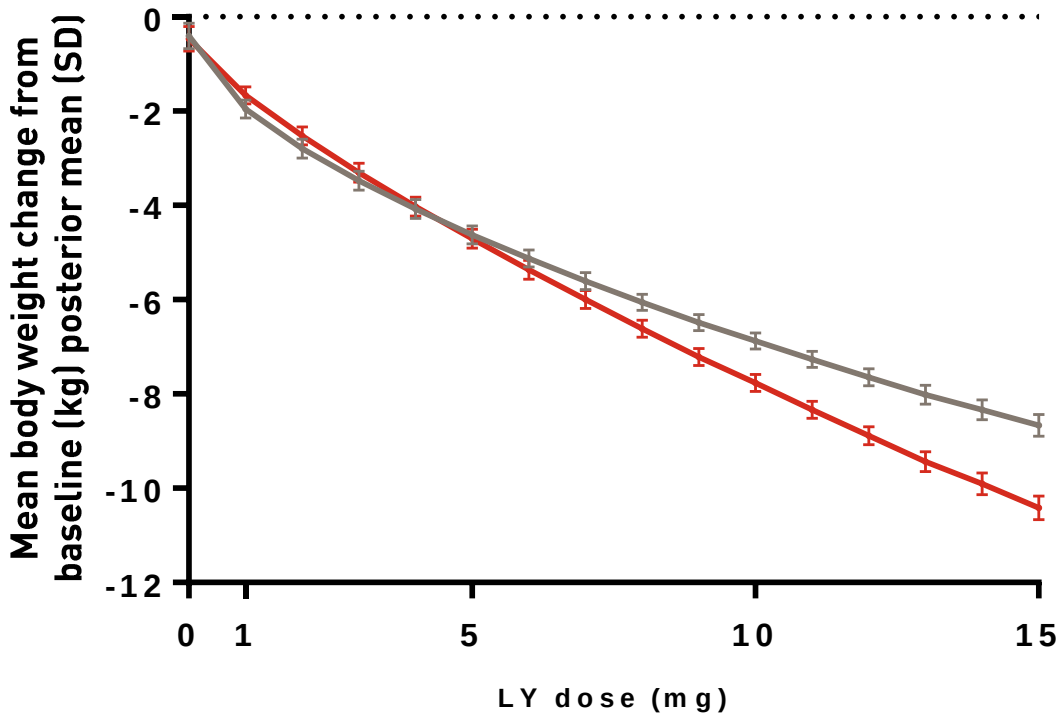
Frias JP et al. *The Lancet.* 2018.

# BAYESIAN DOSE RESPONSE AT 26 WEEKS

## HbA1c (%)




## Weight Loss (Kg)



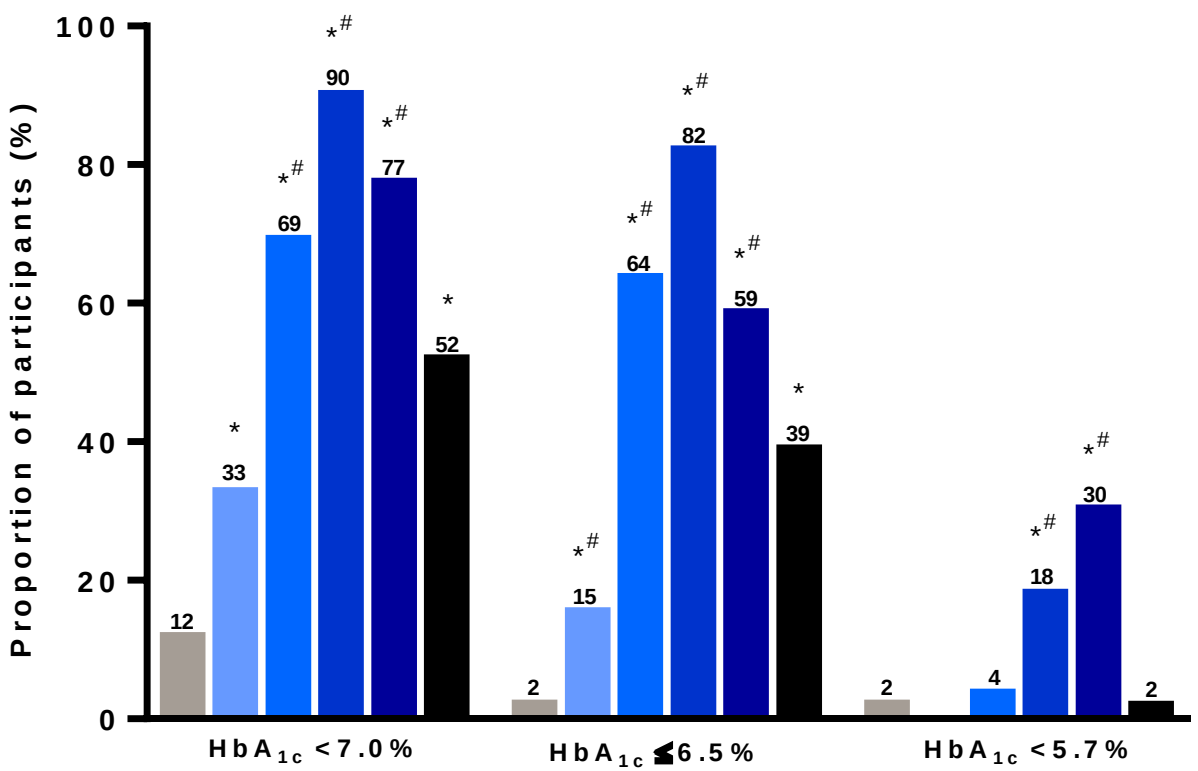

Bayesian dose response model with interpolated dose levels



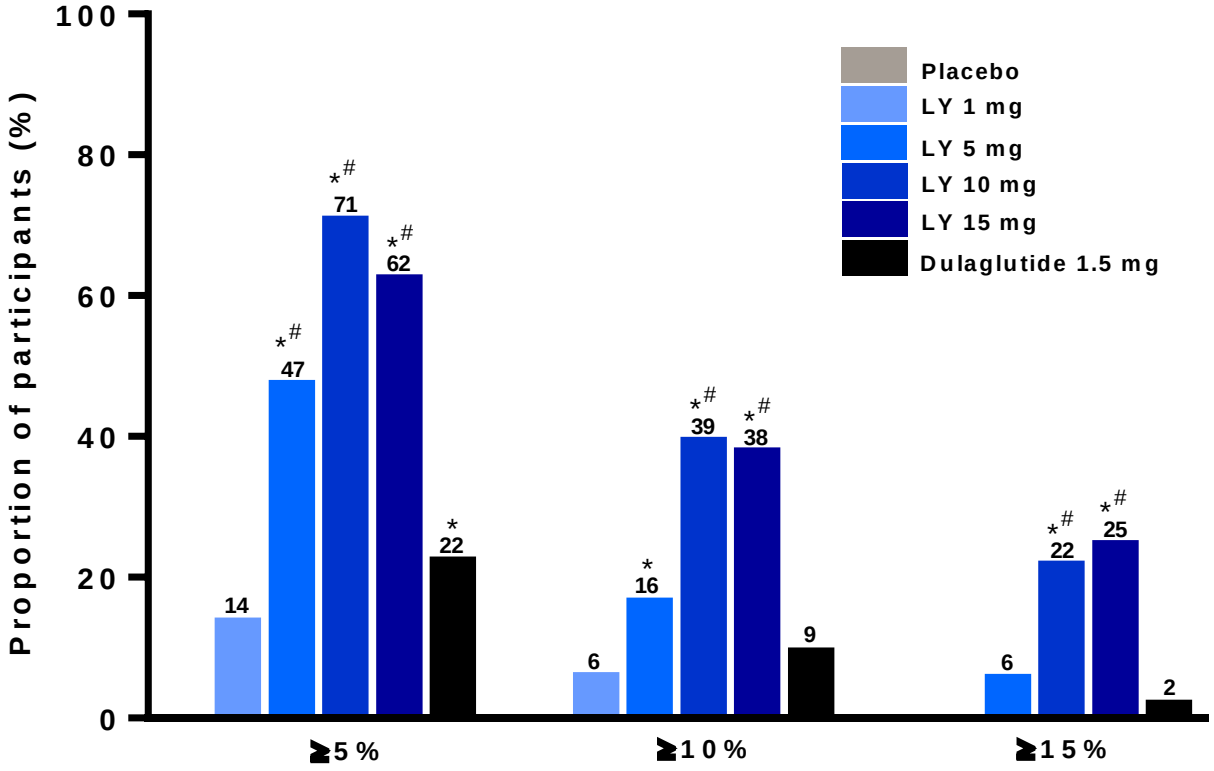
Frias JP et al. *The Lancet.* 2018.

# PROPORTION OF PATIENTS ACHIEVING A1C AND WEIGHT TARGETS AT WEEK 26

## HbA1c (%) Targets




## Weight Loss (%) Targets




**30% of 15 mg dose patients achieve < 5.7% A1c, a mark of normal glucose level**

**25% of 15 mg dose patients achieve >15% body weight reduction,**

logistic regression using LOCF analysis. *,#p<0.05 vs placebo and dulaglutide 1.5 mg, respectively.



Frias JP et al. *The Lancet.* 2018.

# SAFETY AND TOLERABILITY SUMMARY

| | LY 5mg | LY 10mg | LY 15mg | Dula 1.5mg |
|---|---|---|---|---|
| Adverse Events (AE) (%) | 72.7 | 78.4 | 84.9 | 74.1 |
| Serious AEs (%) | 1.8 | 5.9 | 3.8 | 5.6 |
| Discontinued Treatment due to AE (%) | 9.1 | 5.9 | 24.5 | 11.1 |
| Nausea (%) | 20.0 | 21.6 | 39.6 | 29.6 |
| Diarrhea (%) | 23.6 | 23.5 | 32.1 | 16.7 |
| Vomiting (%) | 7.3 | 15.7 | 26.4 | 9.3 |
| Hypoglycemia* (%) | 7.3 / 1.8 | 9.8 / 5.9 | 7.5 / 5.7 | 3.7 / 3.7 |
| Pancreatitis (n) | 2 | 0 | 0 | 0 |
| Cholecystitis (n) | 0 | 1 | 0 | 1 |

* Hypoglycemia (≤70 mg/dL) reported as total / documented symptomatic. There were no reports of severe hypoglycemia.

[a] study identifier NCT03311724

## LY3298176

- Most common AEs were gastrointestinal (nausea, vomiting, diarrhea); Majority were mild to moderate and transient.
- Treatment discontinuations in the higher dose groups primarily occurred during the titration phase.
- A separate study[a] evaluated slower, step-wise titration, enabling phase 3 design. Discontinuation due to AE was <5% (including 15mg) over the 12 week study period.
- Treatment-emergent ADA in LY3298176-treated patients (titers generally low, no PK/PD correlation).
- Heart rate and blood pressure effects comparable to dulaglutide.

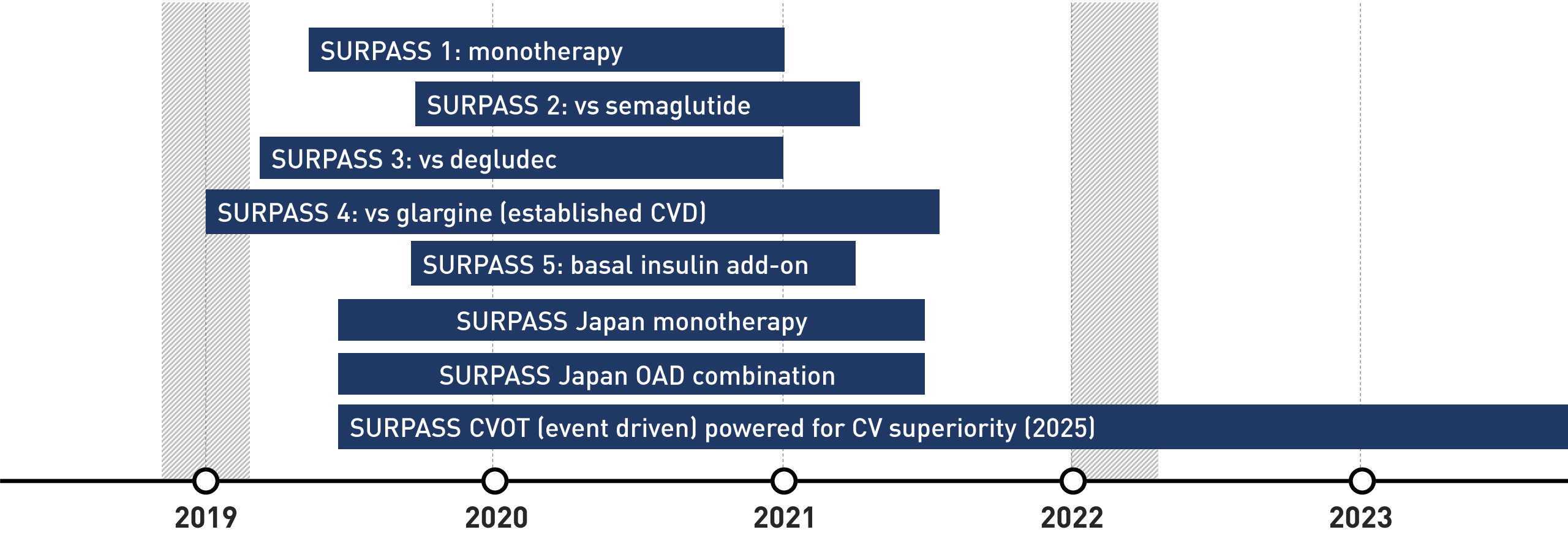


Frias JP et al. *The Lancet.* 2018.

# LY3298176 PHASE 3 T2DM CLINICAL PROGRAM

late 2018 / early 2019
**SURPASS PROGRAM INITIATION**

2022
**POTENTIAL GLOBAL SUBMISSIONS**



# SUMMARY

# LY3298176

Dual GIP/GLP-1 Receptor Agonist

**Next generation once-weekly dual incretin designed to strengthen Lilly's leadership in the first injectable space.**

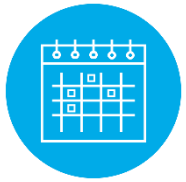
## What We Aim to Do:

**Exceed expectations** for glycemic control and weight reduction


**Replicate** Trulicity's injection experience

**Launch first** with multi-year lead in new class of GIP and GLP-1 receptor dual agonists

**Deliver** meaningful CV benefit



**Target Phase 3** start for late 2018/early 2019


Lilly