
The Future of GLP-1 Therapies, Combinations and New Delivery Systems

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The full data set from LEADER will be presented at ADA in June 2016

Key milestones

Sep 2010: LEADER initiated as a post-approval commitment to the US FDA and EMA

04 Mar 2016: Victoza® significantly reduces the risk of major adverse cardiovascular events in the LEADER trial

June 2016: ADA 2016 – presentation of full dataset from LEADER

H2 2016: Submission of LEADER data to regulatory authorities as part of post-approval commitments

Timeline

Alternate Algorithm

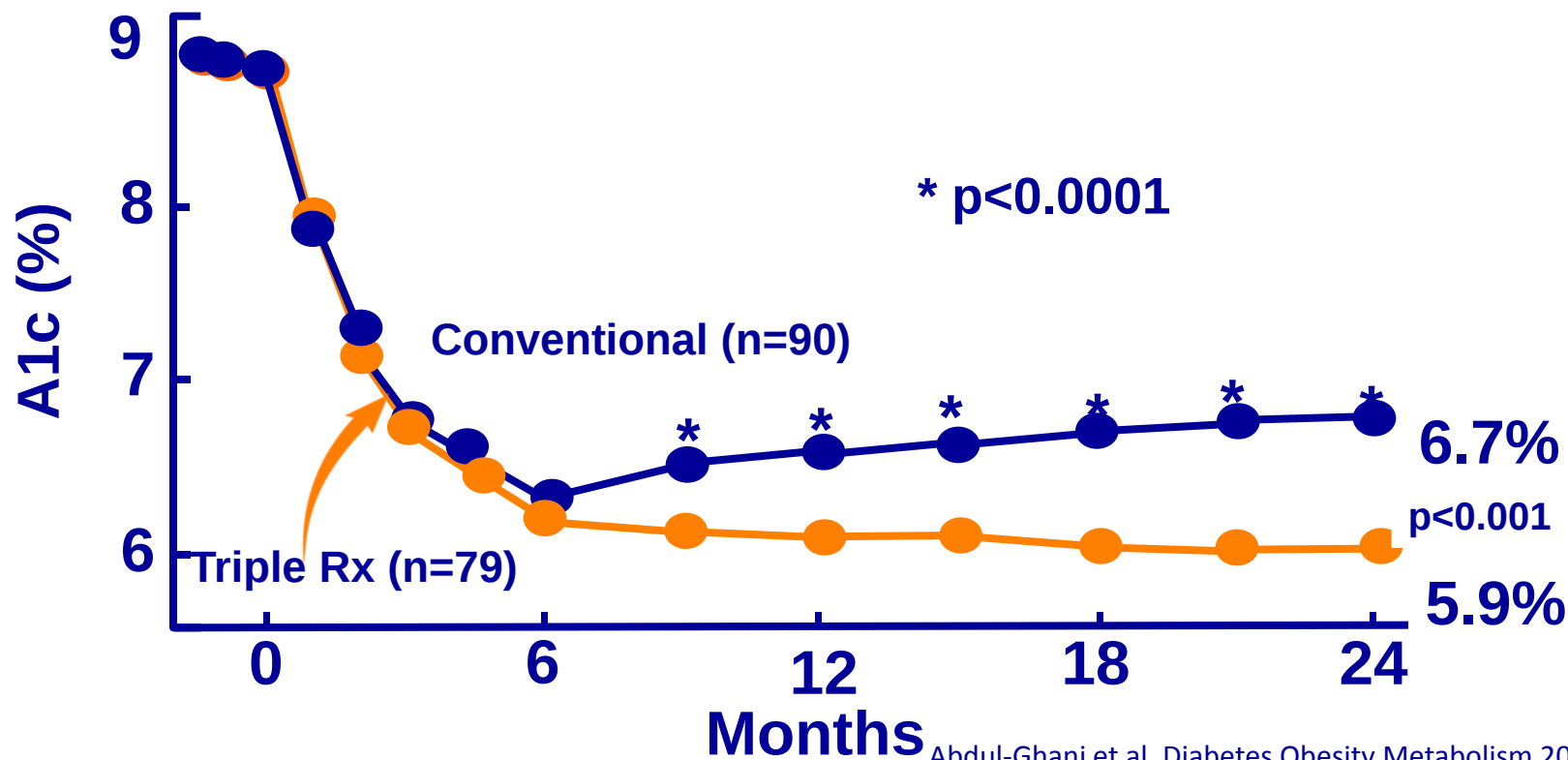
Pathophysiologic-Based Algorithm (DeFronzo)

**Lifestyle +
TRIPLE COMBINATION:
Metformin
+ Pioglitazone
+ GLP-1 Analogue**

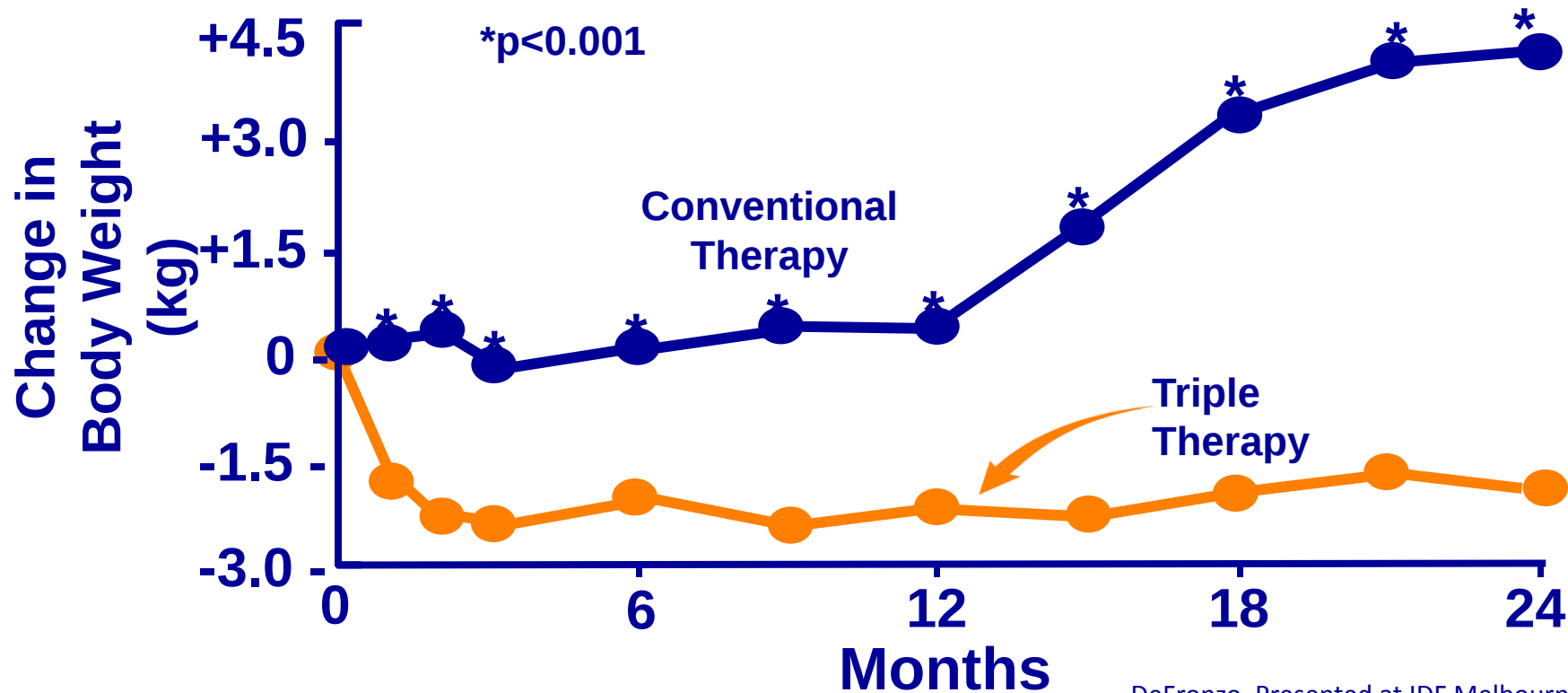


A1c < 6.0%

Time-Related Change in A1c

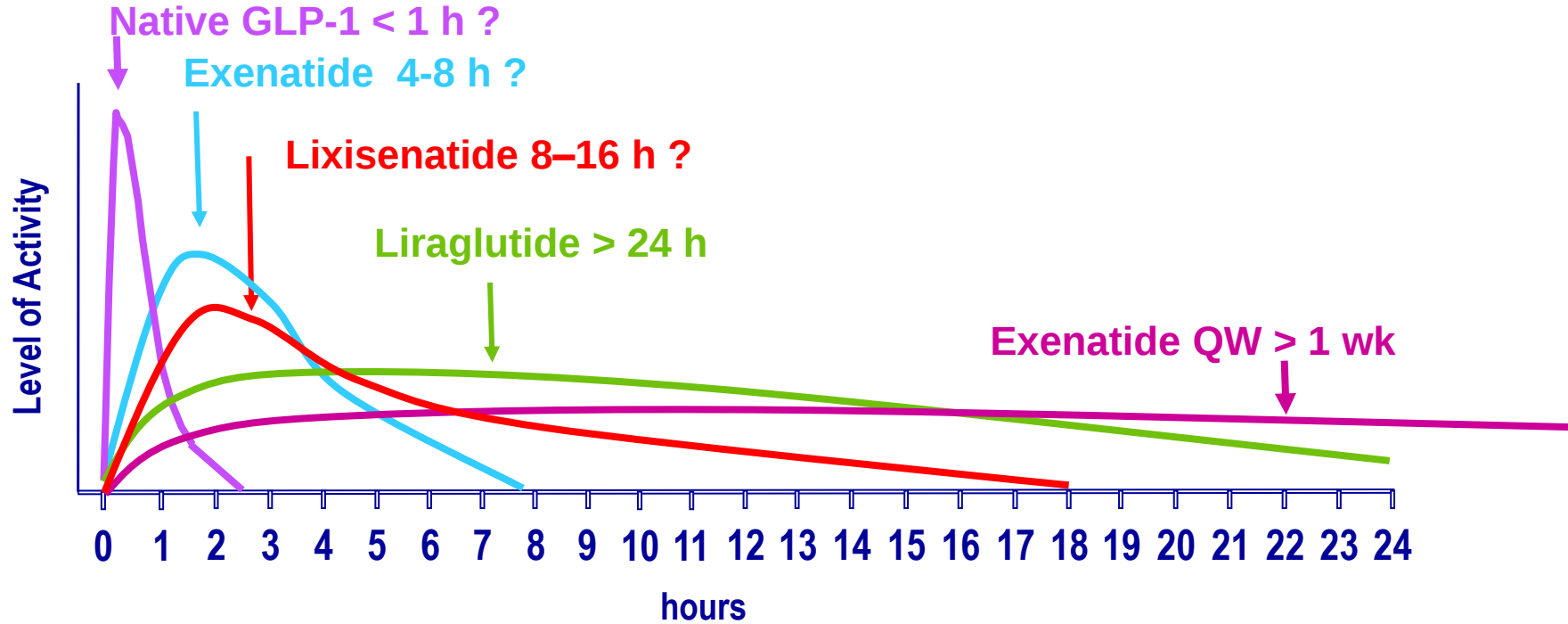


Time-Related Change in Body Weight



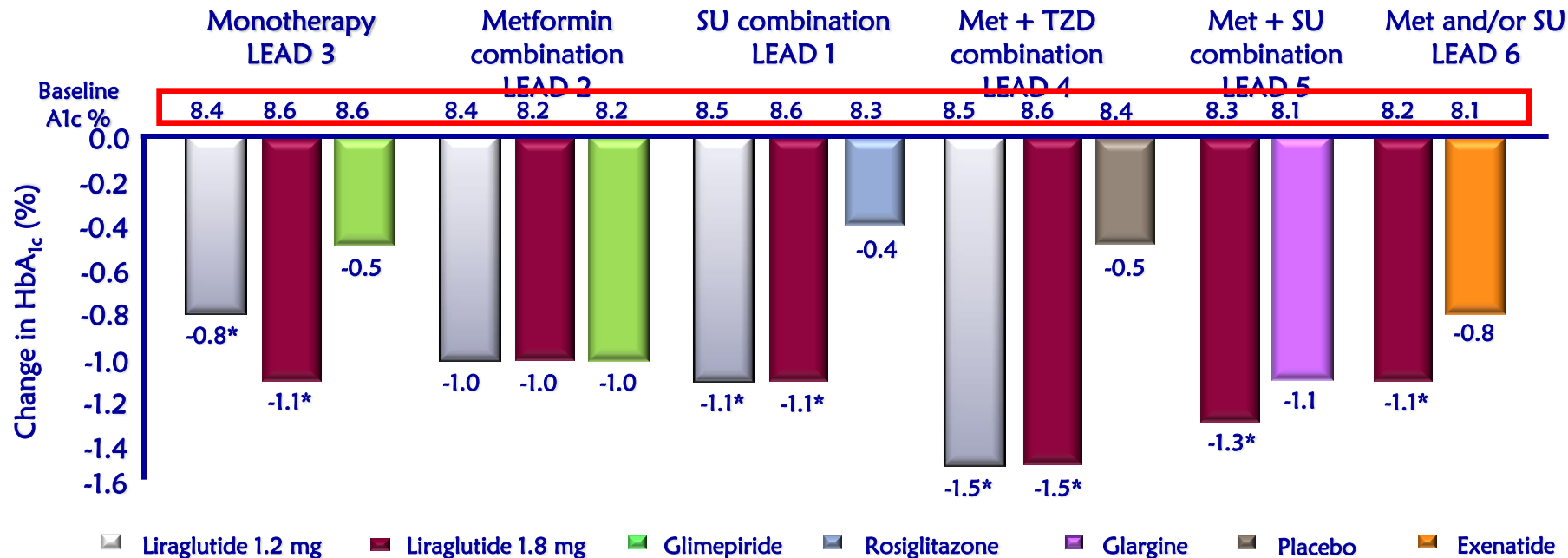
Current Preparations

A Family of GLP-1 Agonists with Different Durations of Action?



A1C Changes with Liraglutide in LEAD Program

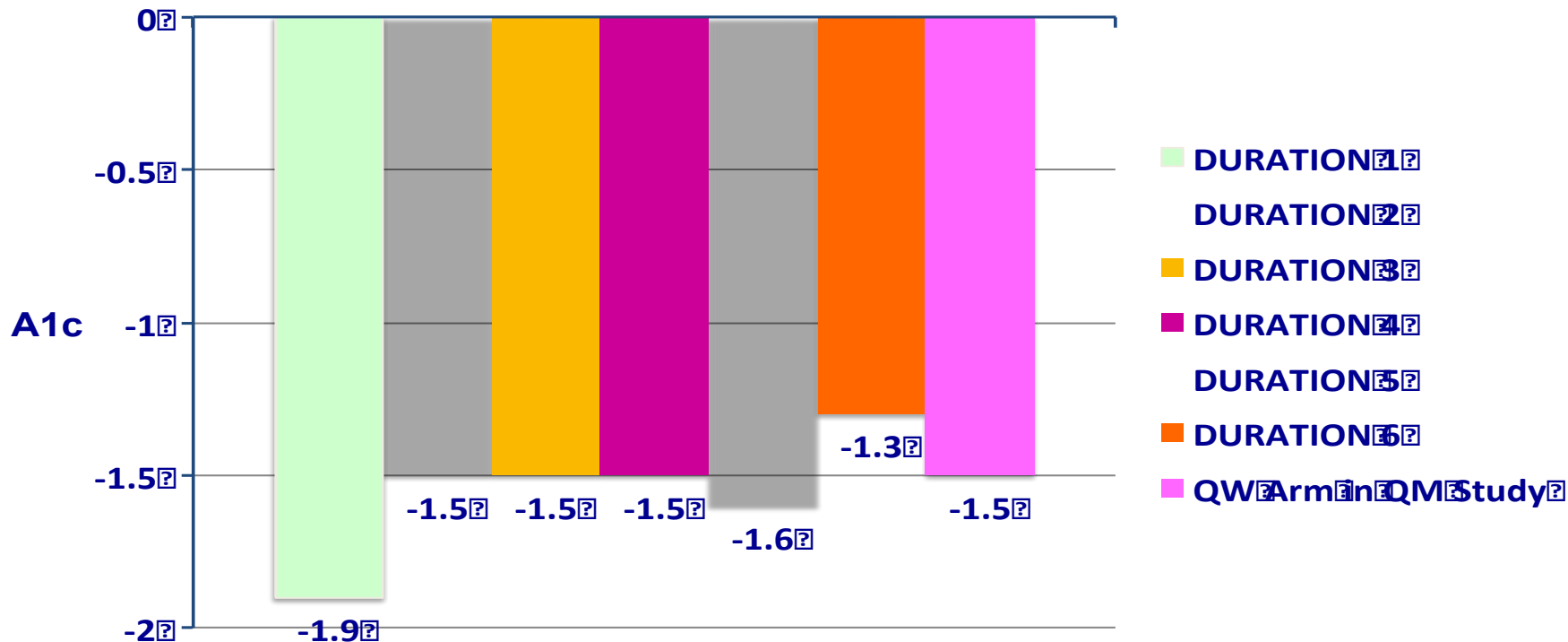
(All Subjects)



*Significant vs. Comparator

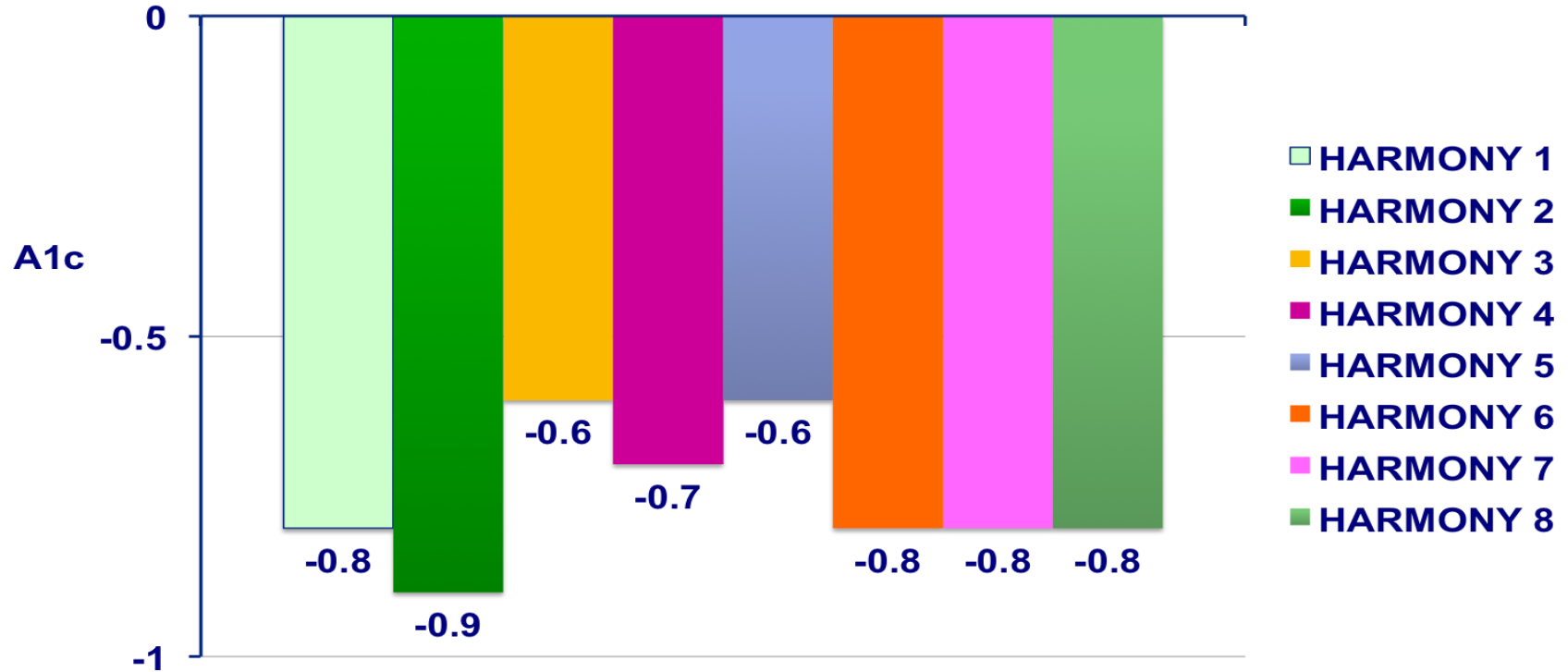
Marre et al. Diabetic Medicine 2009 (LEAD-1); Nauck et al. Diabetes Care 2009 (LEAD-2); Garber et al. Lancet 2009 (LEAD-3); Zinman et al. Diabetologia 2008 (LEAD-4); Russell-Jones et al. Diabetologia 2010 (LEAD 5); Buse et al. Lancet 2009 (LEAD-6).

Exenatide Once Weekly A1c Changes



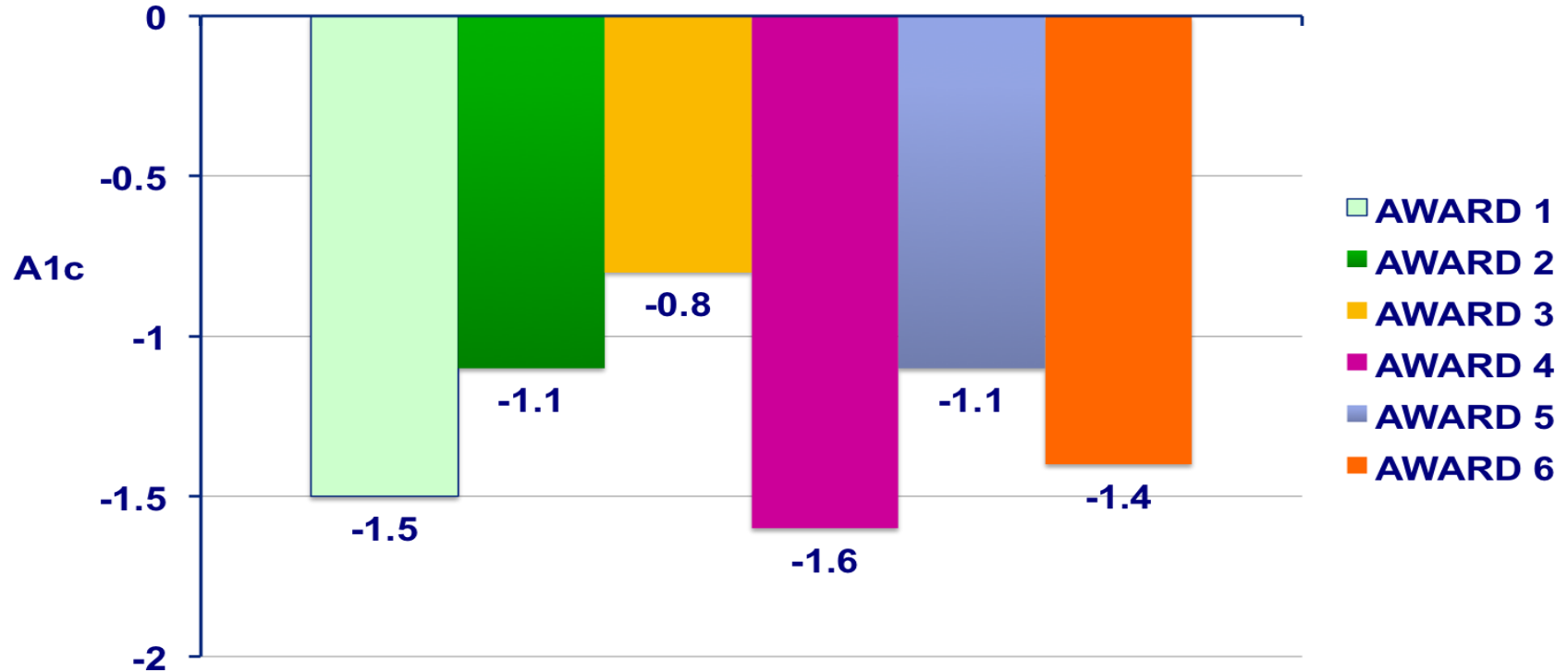
Buse et al. Diabetes Care (DURATION 1). 2010;33:1255-61; Bergenstal et al. Lancet (DURATION 2). 2010;376:431-9; Diamont et al. Lancet (DURATION 3). 2010;375:2234-43; Russell-Jones D et al. Diabetes Care (DURATION 4). 2012;35:252-8; Blevins et al. J Clin Endocrinol Metab (DURATION 5). 2011;96:1301-10; Buse et al. Lancet (DURATION 6). 2013;381:117-24; MacConell et al. Presented at ADA 2011, Late Breaking

Albiglutide Once Weekly A1c Changes



Reusch et al. Diabetes Obes Metab (HARMONY 1). 2014;16:1257-64; Nauck et al. Diabetologia (HARMONY 2). 2016;59(2):266-74; Ahren et al. Diabetes Care (HARMONY 3). 2014;37:2141-8; Weissman et al. Diabetologia (HARMONY 4). 2014 ;57:2475-84; Home et al. Diabetes Obes Metab (HARMONY 5). 2015;17(2):179-87; Rosenstock et al. Diabetes Care (HARMONY 6). 2014;37(8):2317-25; Pratley et al. Lancet Diabetes Endocrinol (HARMONY 7). 2014;2:289-97. Leiter et al. Diabetes Care (HARMONY 8). 2014;37:2723-30.

Dulaglutide Once Weekly A1c Changes

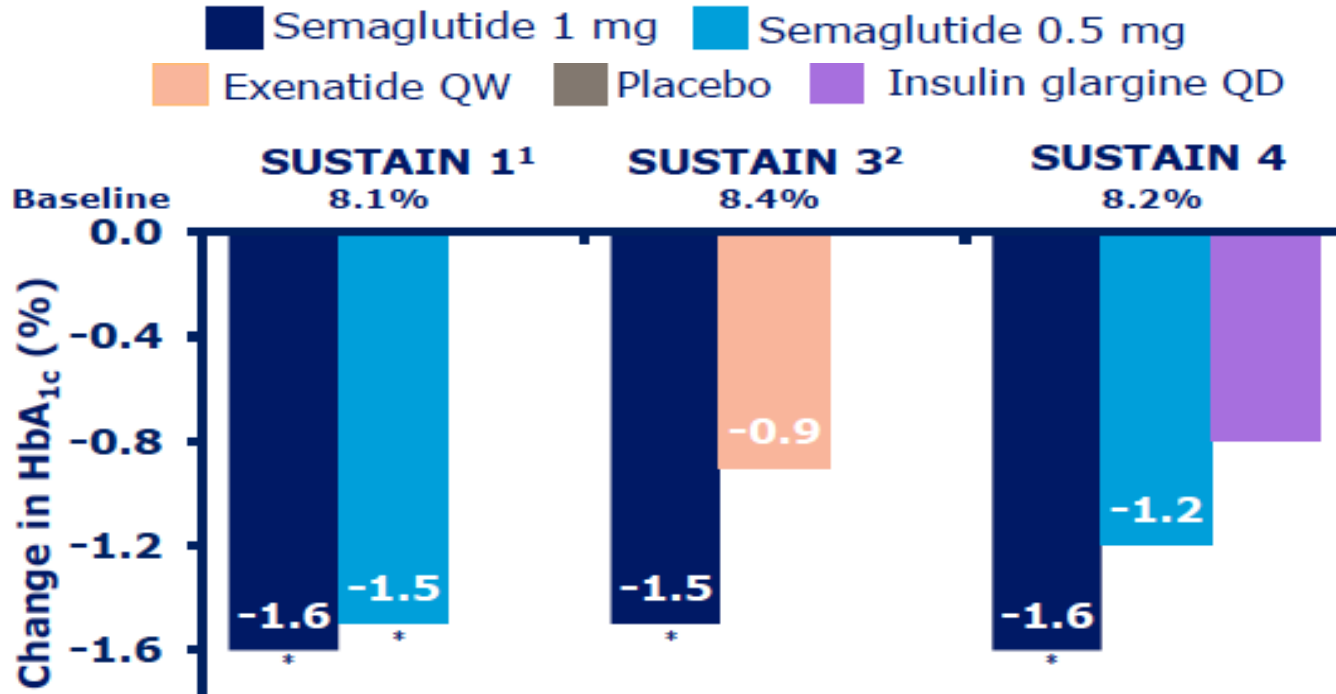


Wysham et al. Diabetes Care (AWARD 1). 2014;37:2159-67; Giorgino et al. Diabetes Care (AWARD 2). 2015;38:2241-9; Umpierrez et al. Diabetes Care (AWARD 3). 2014;37:2168-76; Blonde et al. Lancet (AWARD 4). 2015;385:2057-66; Weinstock et al. Diabetes Obes Metab (AWARD 5). 2015;17:849-58; Dungan et al. Lancet (AWARD 6). 2014;384:1349-57.

New Preparations

Weekly Semaglutide*

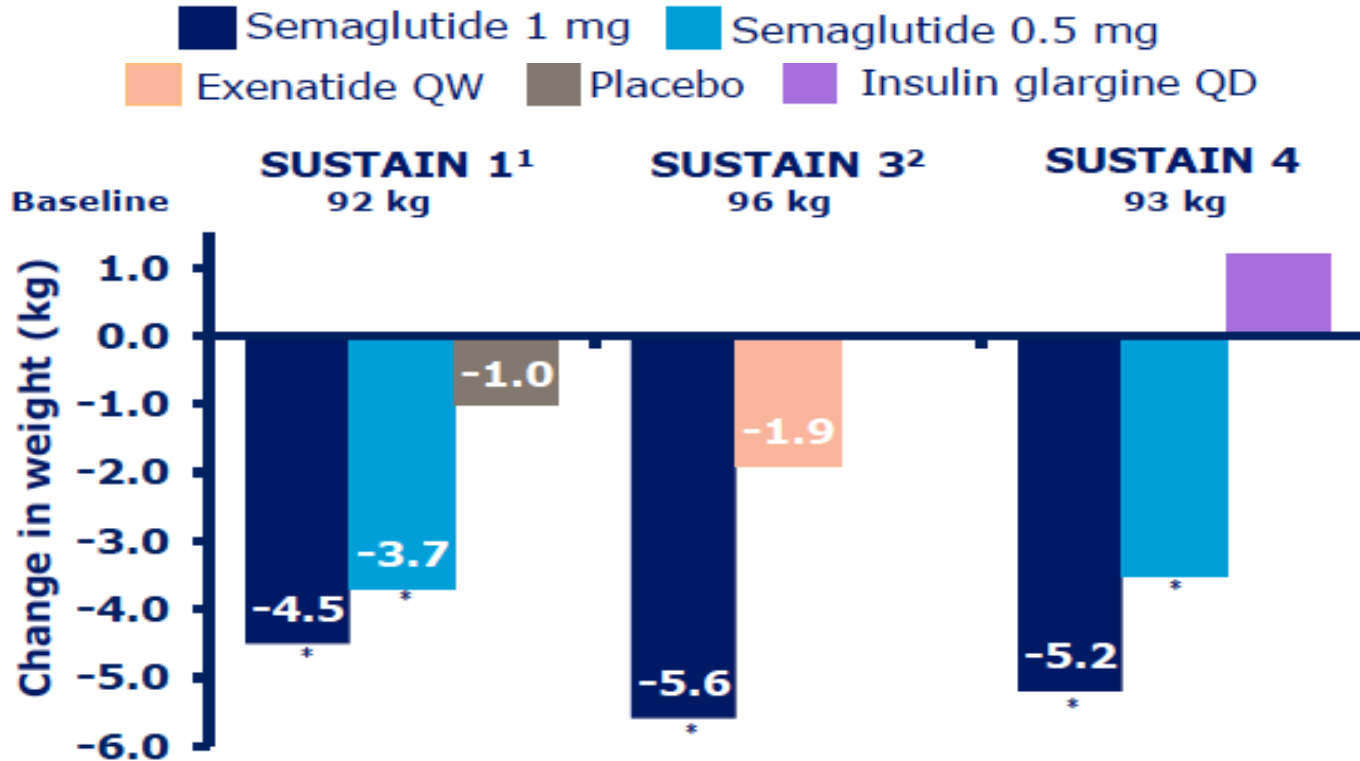
A1c Change



*Not FDA approved

Weekly Semaglutide*

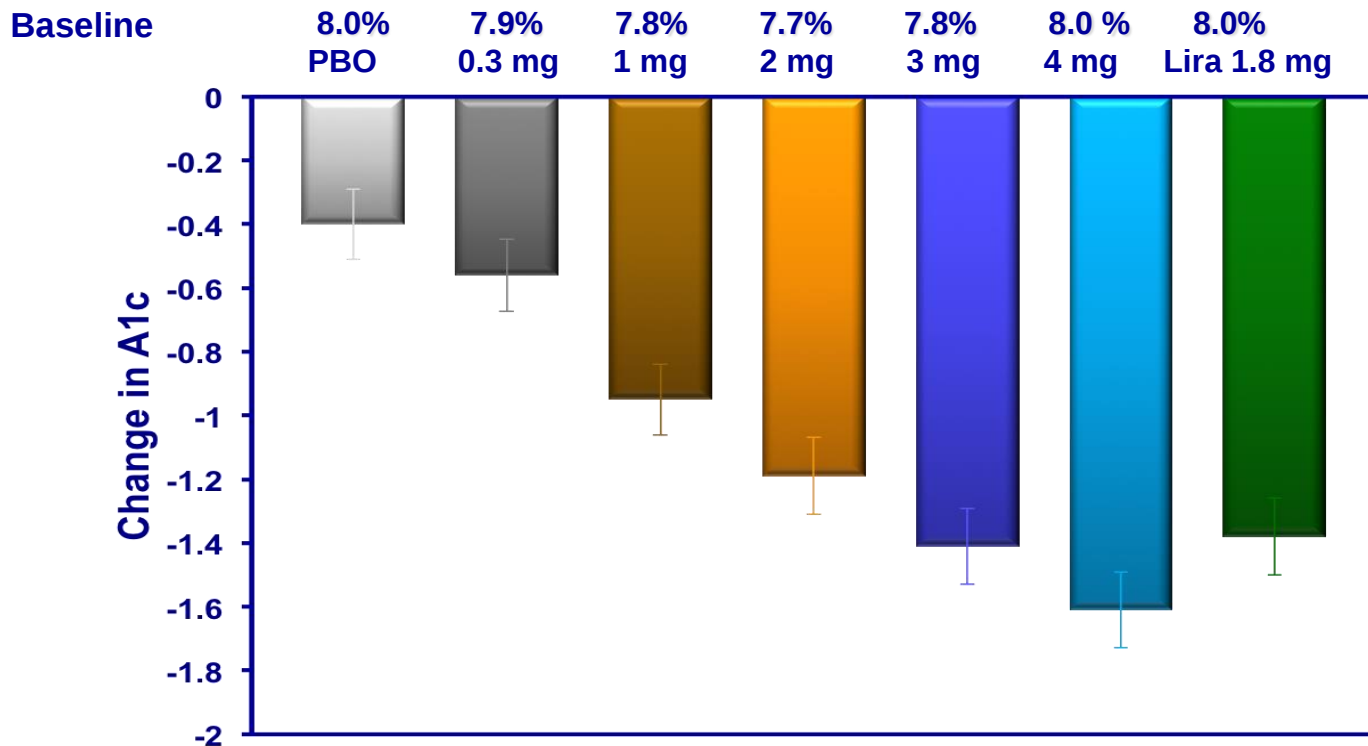
Body Weight Change



*Not FDA approved

Weekly Efpeglenatide* Dose Response

A1c Change at Week 13

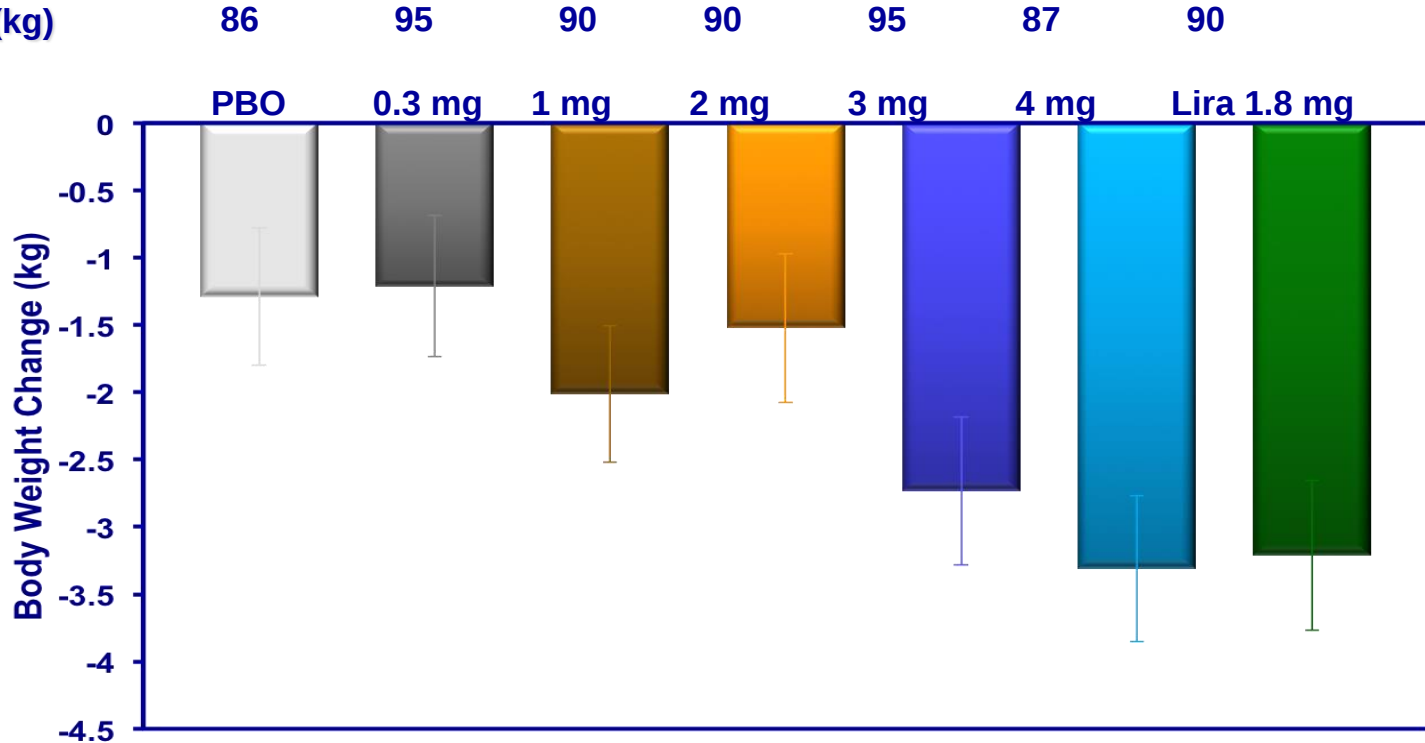


*Not FDA approved

Rosenstock et al. [ADA abstract]. Diabetes. 2015; 64(suppl 1):278-OR.

Weekly Efpeglenatide* Dose Response

Body Weight Change at Week 13

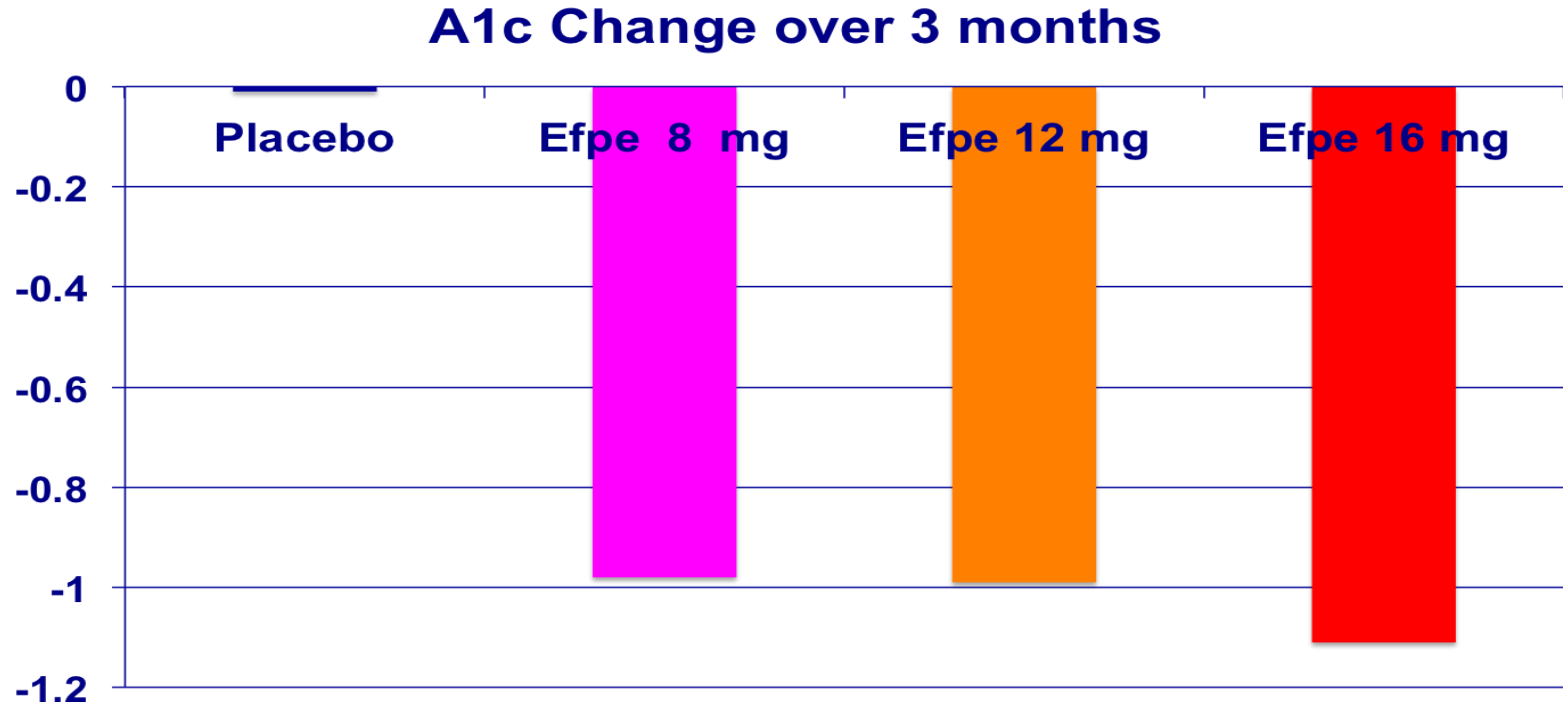


*Not FDA approved

Rosenstock et al. [ADA abstract]. Diabetes. 2015; 64(suppl 1):278-OR.

Monthly Preparations

Monthly Efpeglenatide* Dose Response

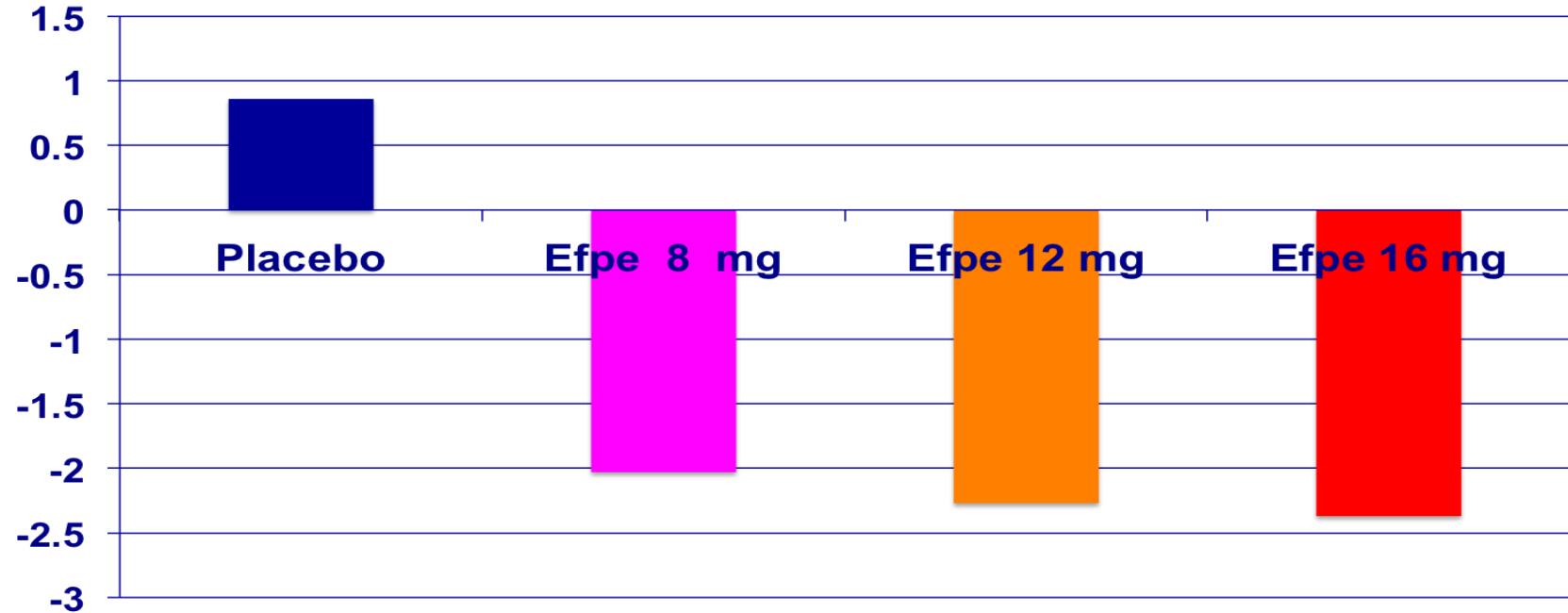


*Not FDA approved

Del Prato et al. Presented at EASD 2015 – Abstract 113

Monthly Efpeglenatide* Dose Response

Body Weight Change over 3 months

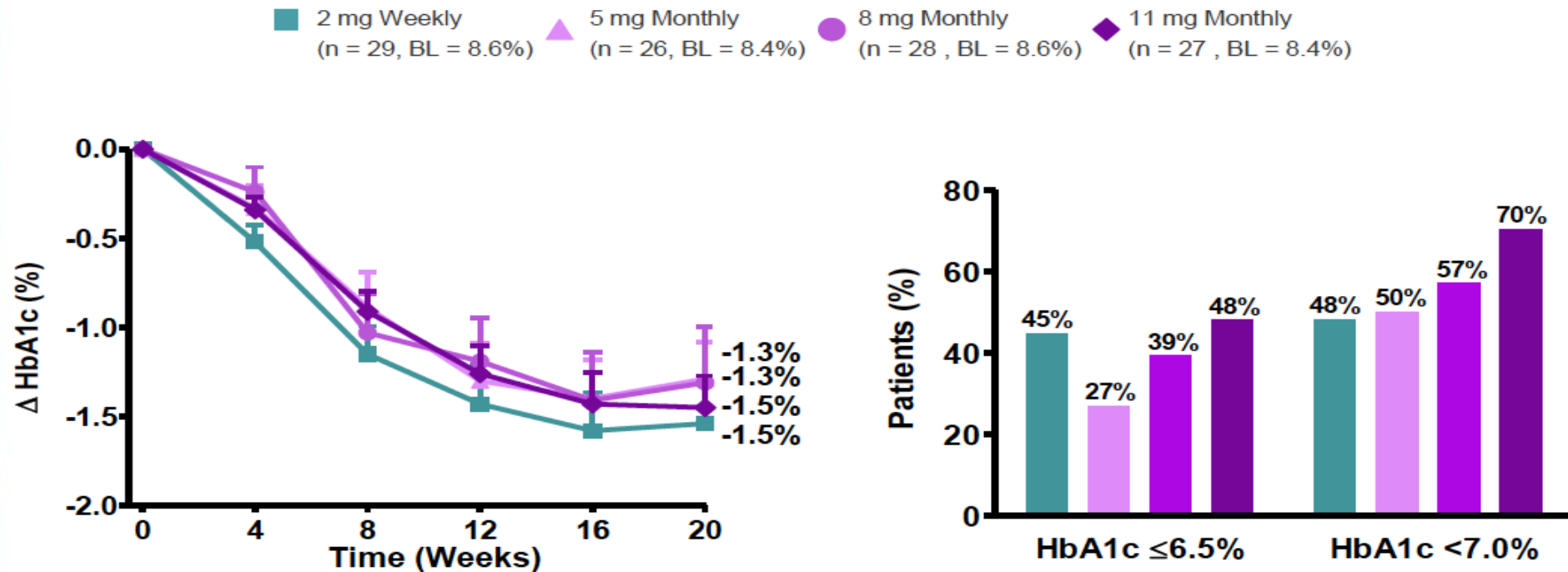


*Not FDA approved

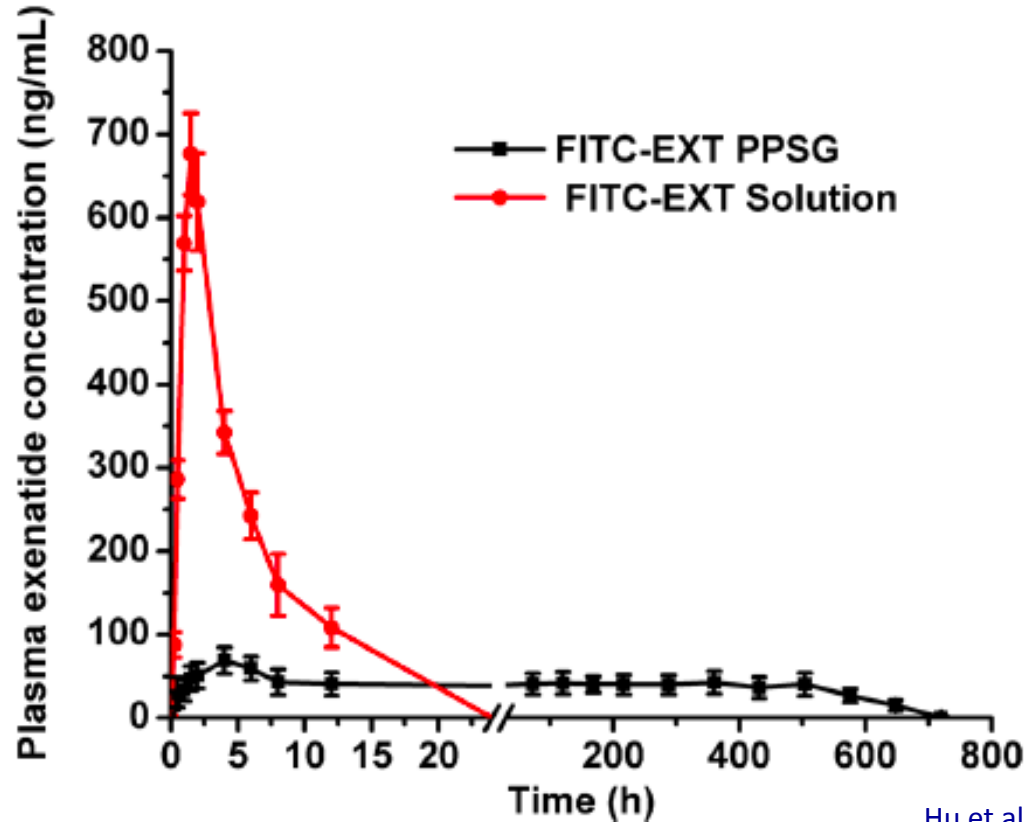
Del Prato et al. Presented at EASD 2015 – Abstract 113

Exenatide Once Monthly

Improvements in HbA1c at Week 20



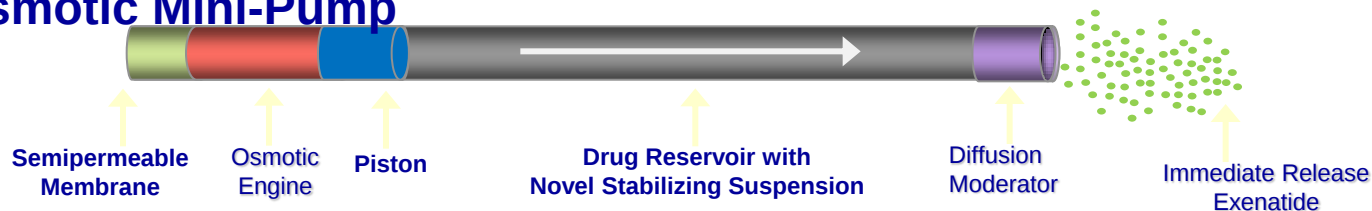
Exenatide Once Monthly Phospholipid Gel Formulation in Rats



Implanted Preparation

Continuous Subcutaneous Exenatide with ITCA 650* Intarcia Delivery Technology

■ Osmotic Mini-Pump

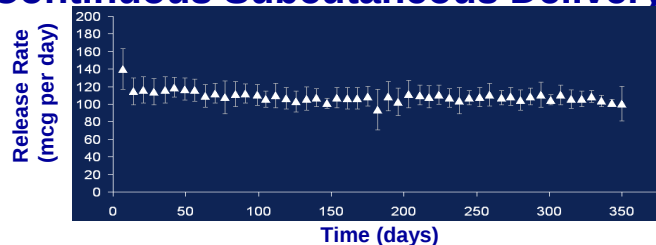


■ Mini-Pump Size of a matchstick!



- ✓ Sub-dermal placement once/twice yearly
- ✓ Done in a brief, in-office, sterile procedure by MD or NP/PAs
- ✓ Approved reimbursement codes for similar procedures

■ Continuous Subcutaneous Delivery of Exenatide



- ✓ Continuous zero order delivery for up to a full 12 months
- ✓ Novel formulation stabilizes peptides at body temps for years

* In development

Intarcia Website – Accessed Jan 18 2016

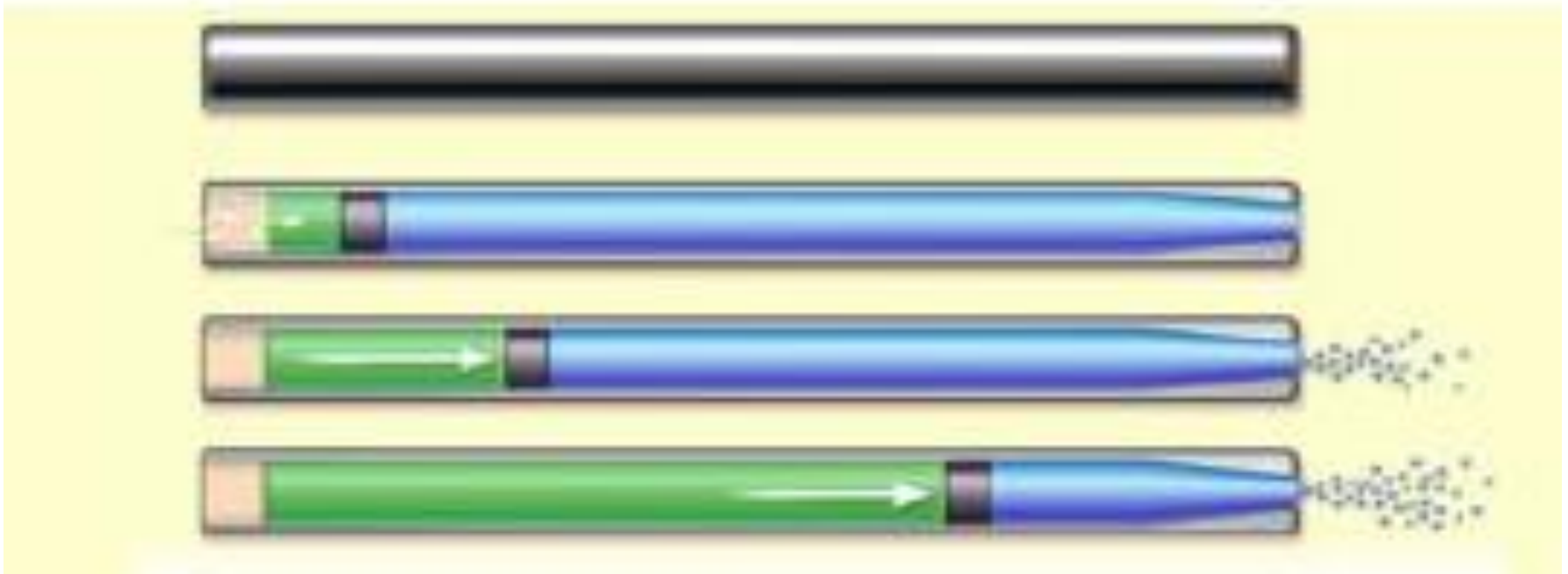
Continuous Subcutaneous Exenatide with ITCA 650* Intarcia Delivery Technology



*In development

Intarcia Website – Accessed Jan 18 2016

Continuous Subcutaneous Exenatide with ITCA 650* Intarcia Delivery Technology

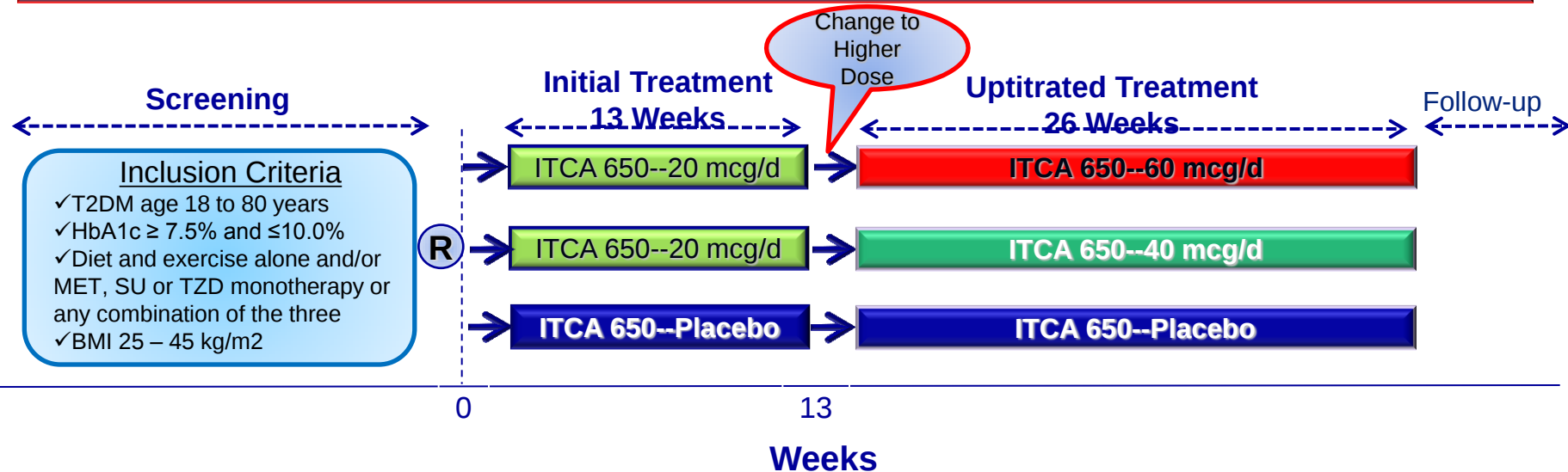


* In development

Intarcia Website – Accessed Jan 18 2016

Continuous Subcutaneous Exenatide with ITCA 650* in Type 2 DM Study Design

Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter 39-Week Study

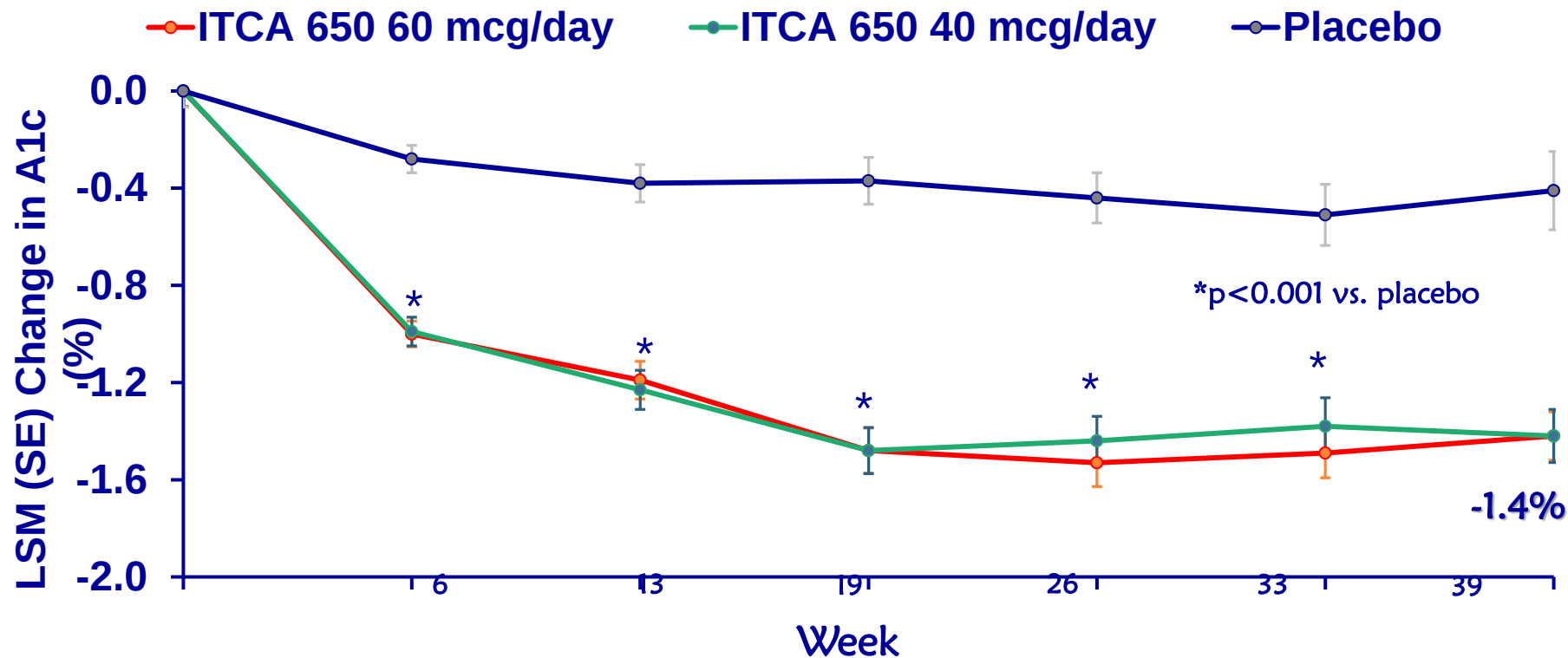


*In development

Rosenstock et al. [ADA abstract]. Diabetes. 2015; 64(suppl 1):276-OR.

Continuous Subcutaneous Exenatide with ITCA 650* in Type 2 DM

A1c Changes Over Time

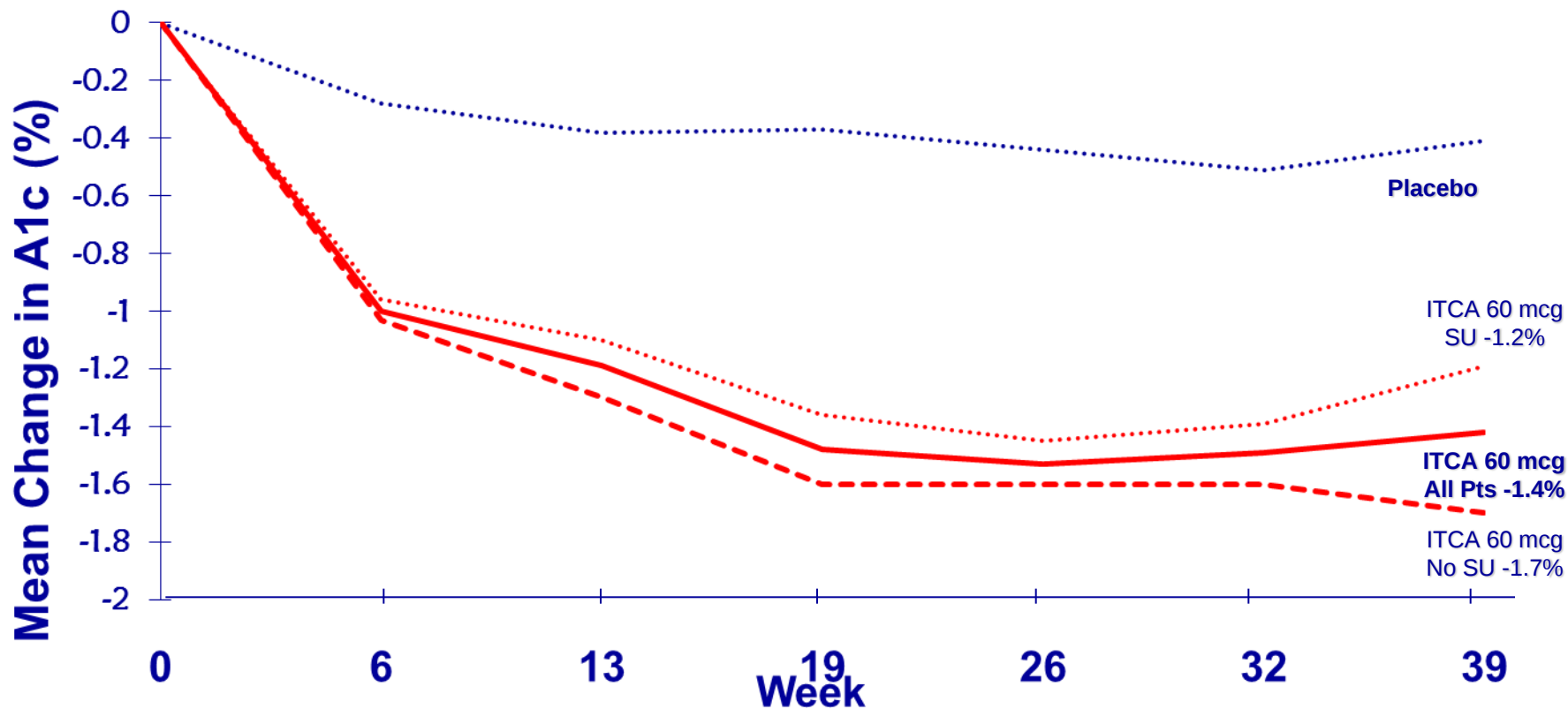


mITT Population

*In development

Rosenstock et al. [ADA abstract]. Diabetes. 2015; 64(suppl 1):276-OR.

Continuous Subcutaneous Exenatide with ITCA 650* in Type 2 DM A1c Changes According to SU Treatment



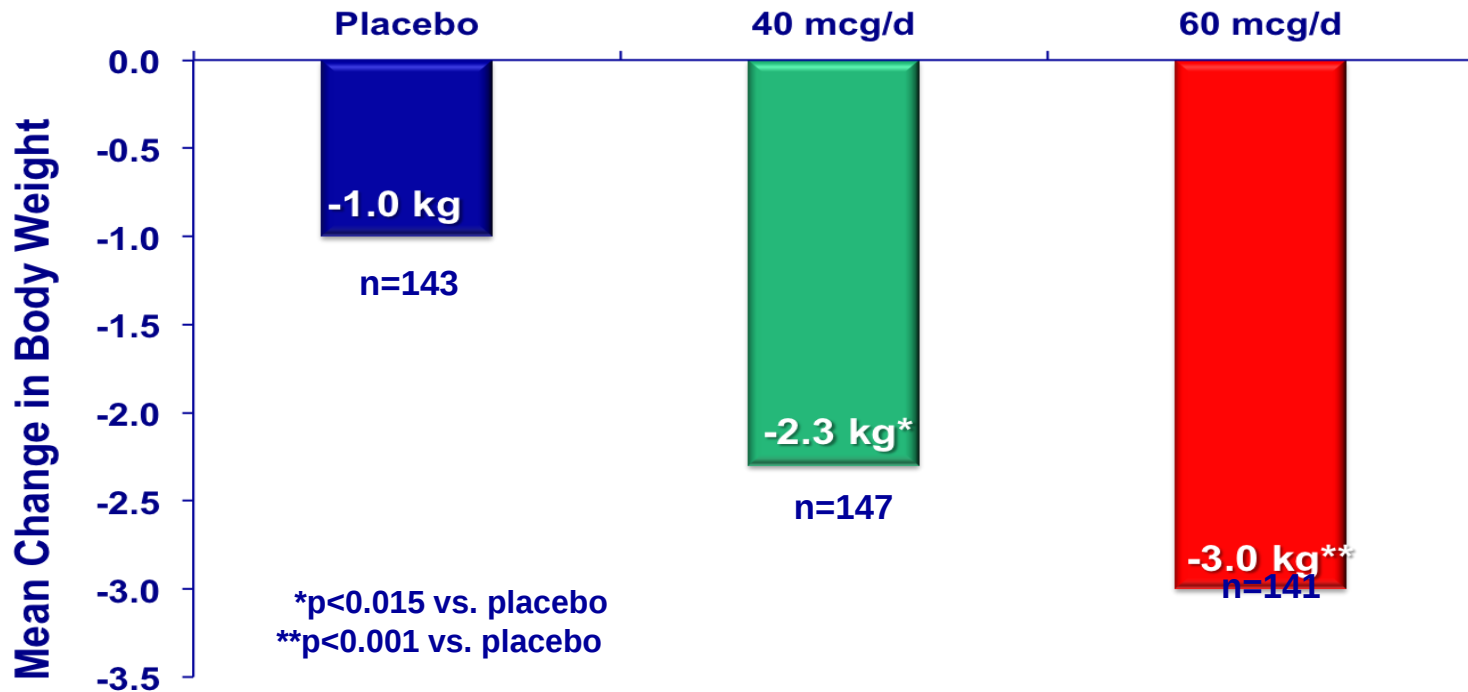
MITT Population

*In development

Rosenstock et al. [ADA abstract]. Diabetes. 2015; 64(suppl 1):276-OR.

Continuous Subcutaneous Exenatide with ITCA 650* in Type 2 DM

Body Weight Changes at Week 39

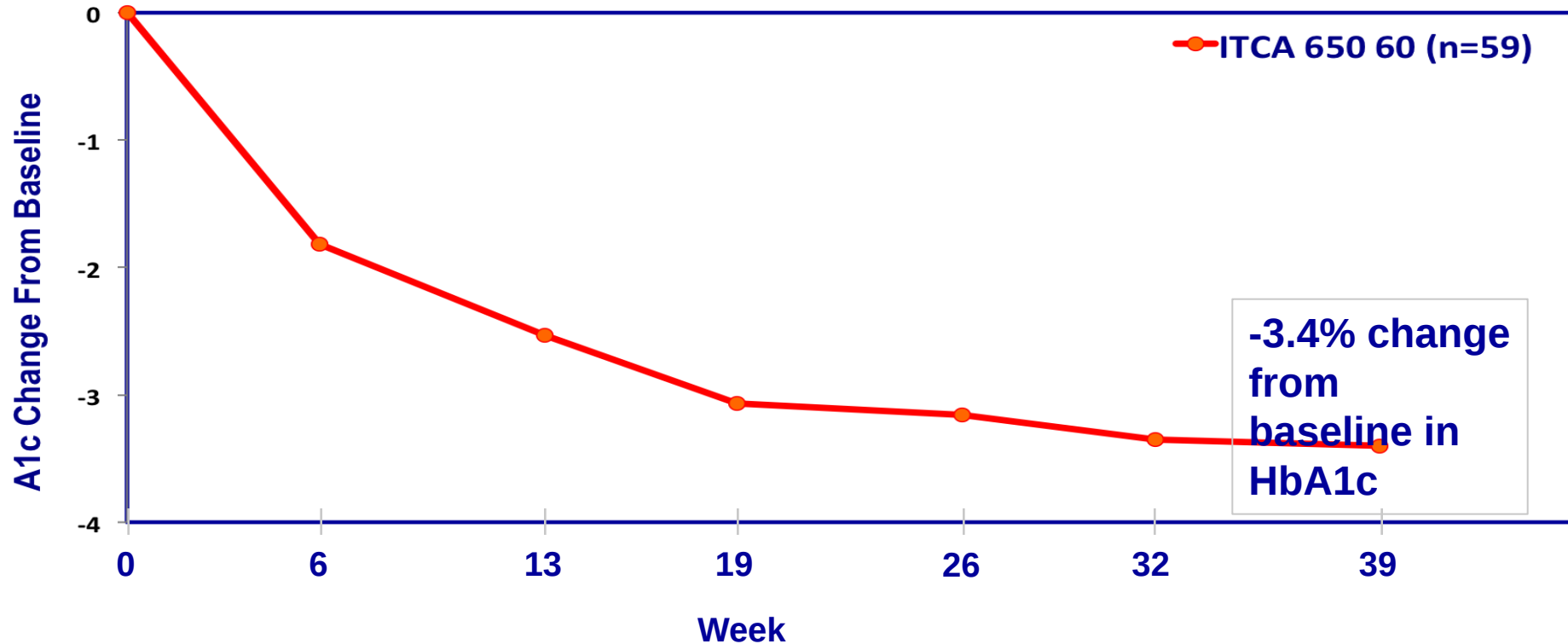


mITT Population

*In development

Rosenstock et al. [ADA abstract]. Diabetes. 2015; 64(suppl 1):276-OR.

Continuous Subcutaneous Exenatide with ITCA 650* in Type 2 DM Change From Baseline in A1c by Visit (Baseline A1c 10-12%)



*In development

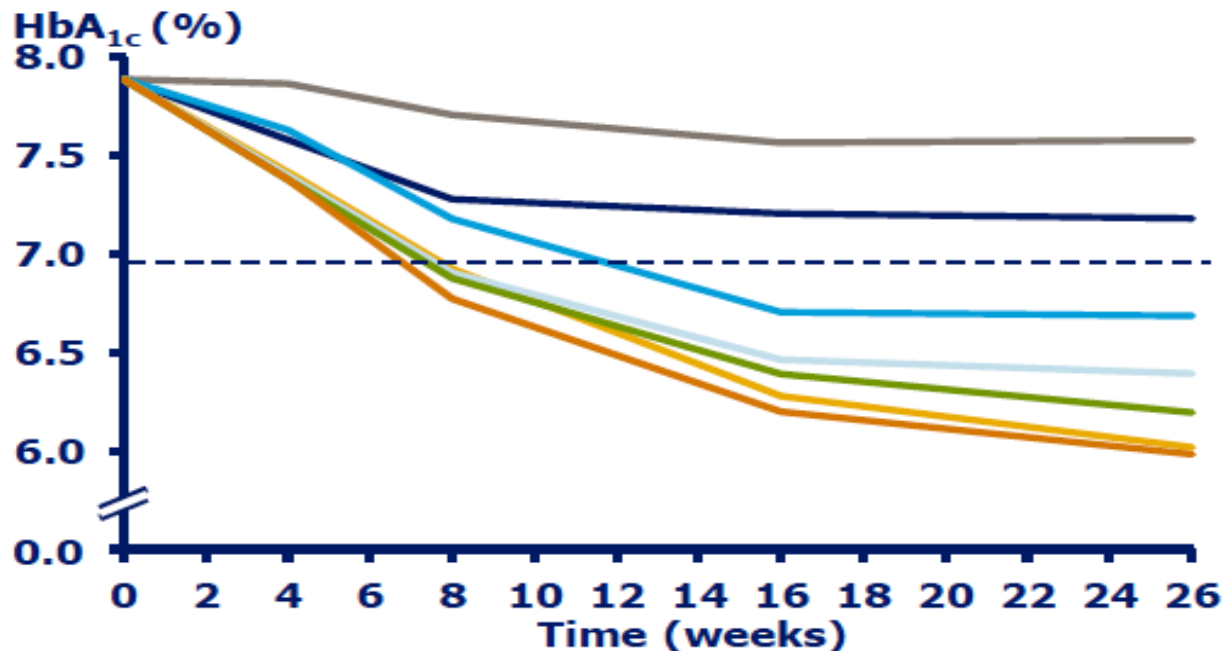
Henry et al. [ADA abstract]. Diabetes. 2015; 64(suppl 1):xxx-P.

Oral Preparations

Oral Semaglutide*

Dose Dependent Change in A1c

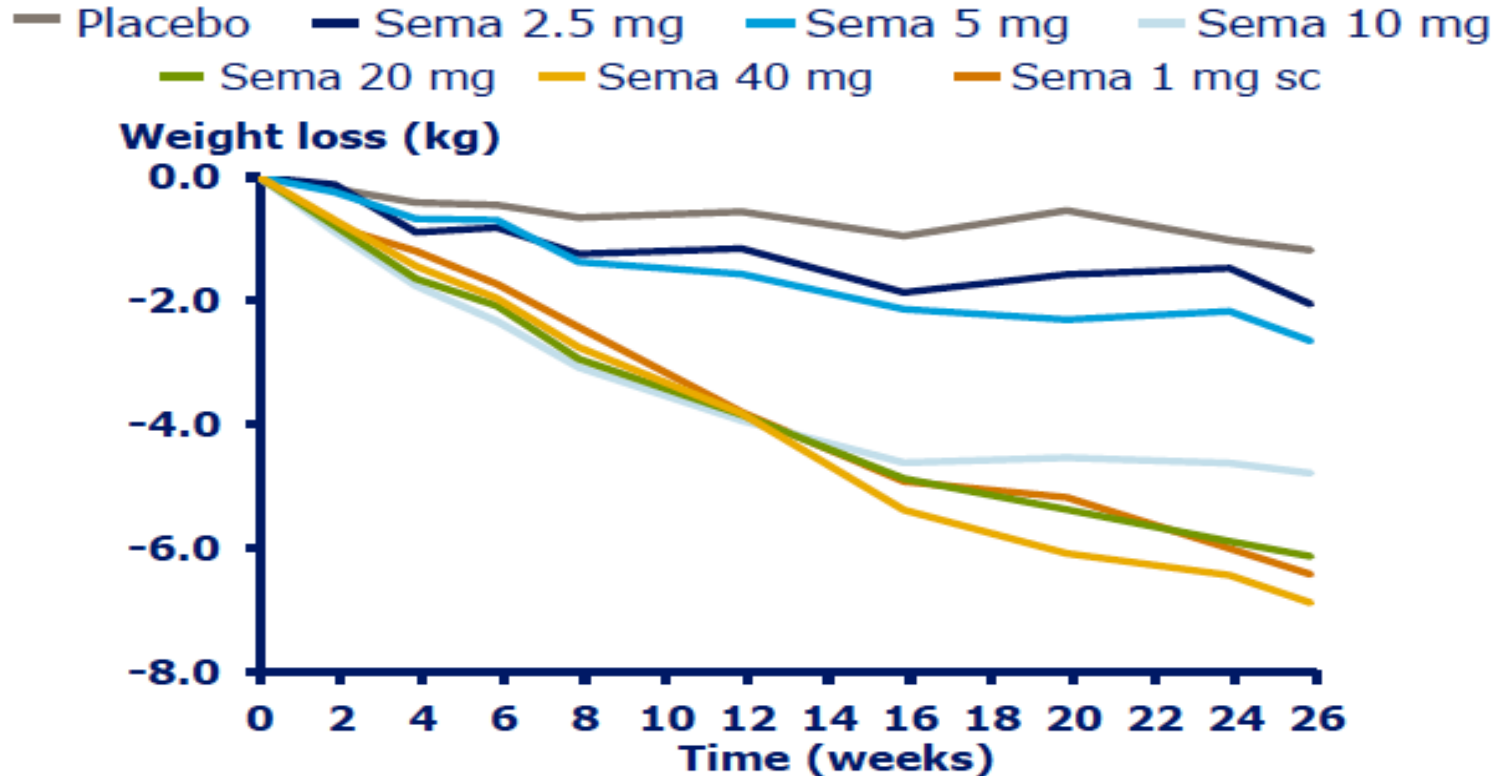
— Placebo — Sema 2.5 mg — Sema 5 mg — Sema 10 mg
— Sema 20 mg — Sema 40 mg — Sema 1 mg sc



Inclusion criteria: Type 2 diabetes; $7.0\% \leq \text{HbA}_{1c} \leq 9.5\%$; treatment with diet and exercise with or without metformin; sc: subcutaneous; sema: semaglutide
Source: Novo Nordisk on file (NN9924-3790)

Oral Semaglutide*

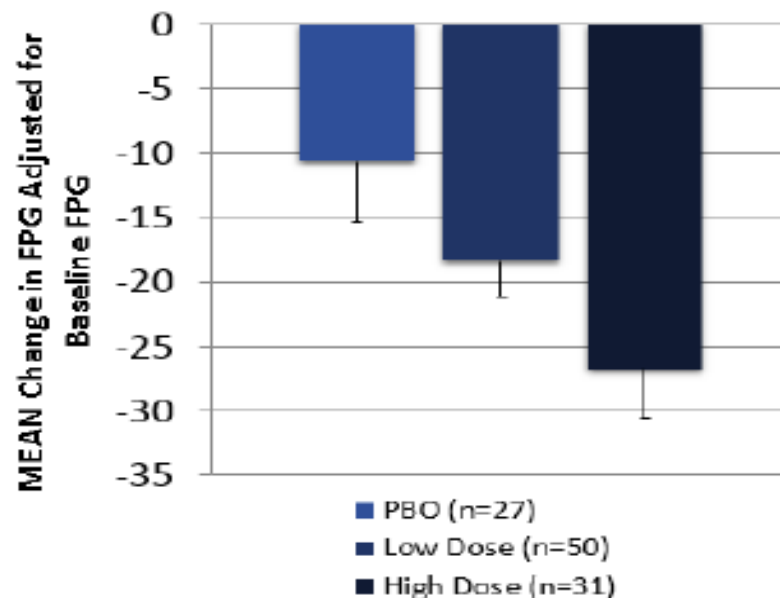
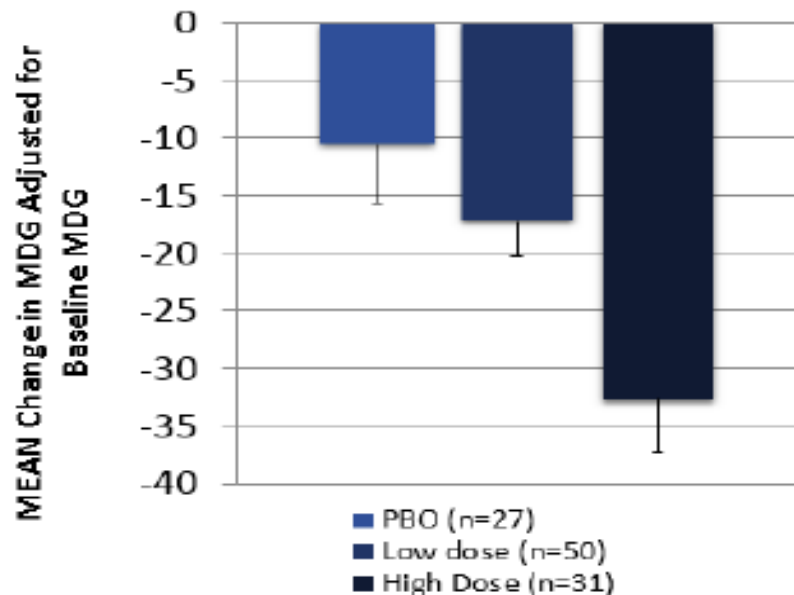
Dose Dependent Change in Body Weight



Oral TTP273 – Non-Peptide GLP1-RA

Dose Dependent Change in Glucose

Phase 1 Trial

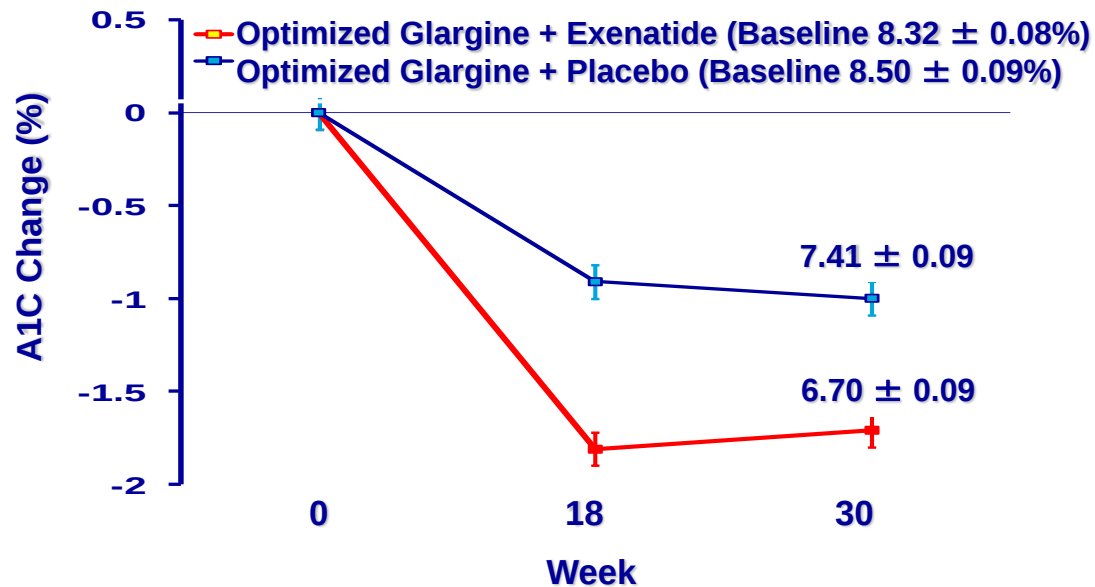


Groups defined by daily dose: PBO, Low dose (<150mg) or High dose (≥150mg)

GLP-1 Insulin Combination Therapy

Add-On Exenatide to Insulin Glargine-Treated Type 2 Diabetes

A1C Change From Baseline



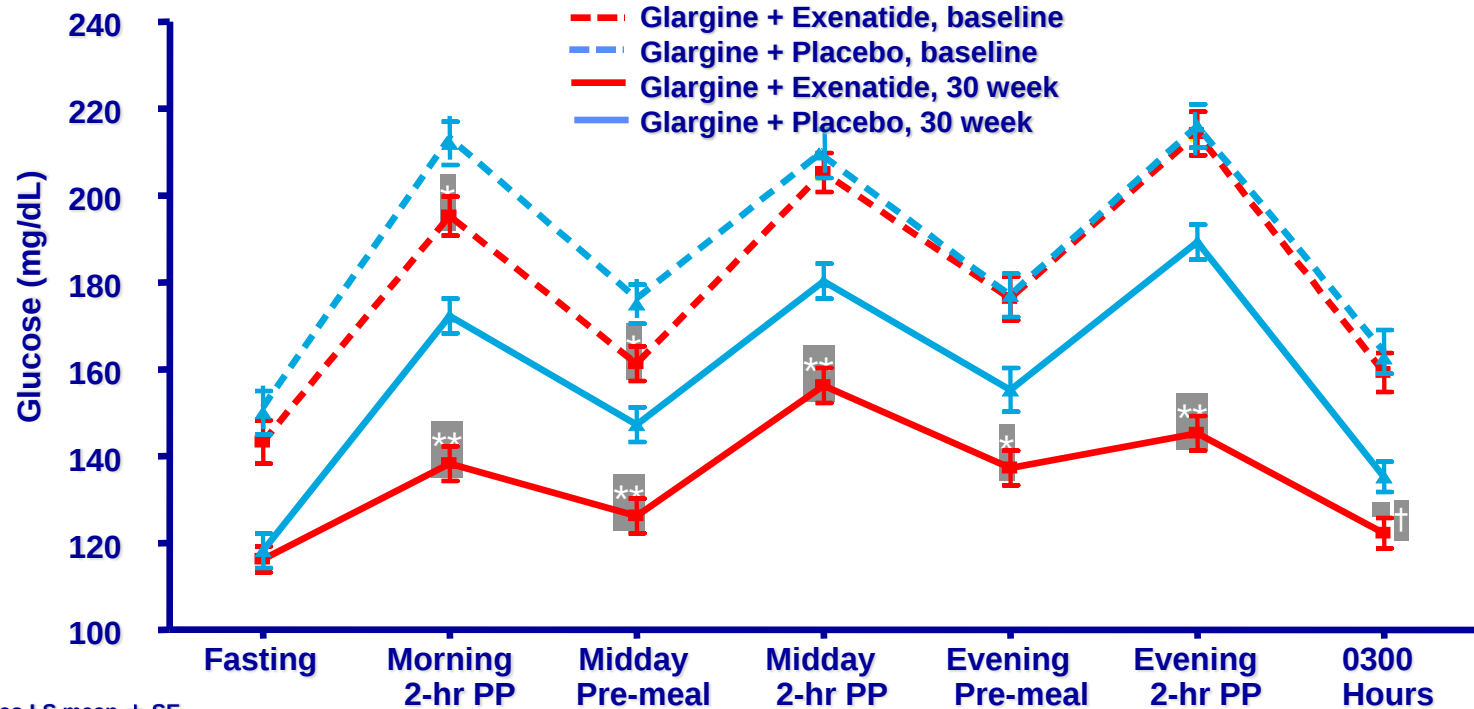
Reduction of A1C from baseline with exenatide BID (optimized glargine and exenatide) was greater than placebo (optimized glargine alone)

-1.71 ± 0.09% vs -1.00 ± 0.09% (Diff, -0.71%; 95% CI, -0.95 to -0.47; P<0.001)

Data presented as LS mean ± SE.

Add-On Exenatide to Insulin Glargine-Treated Type 2 Diabetes

Seven-Point Glucose Profiles



Data presented as LS mean $\pm$ SE.

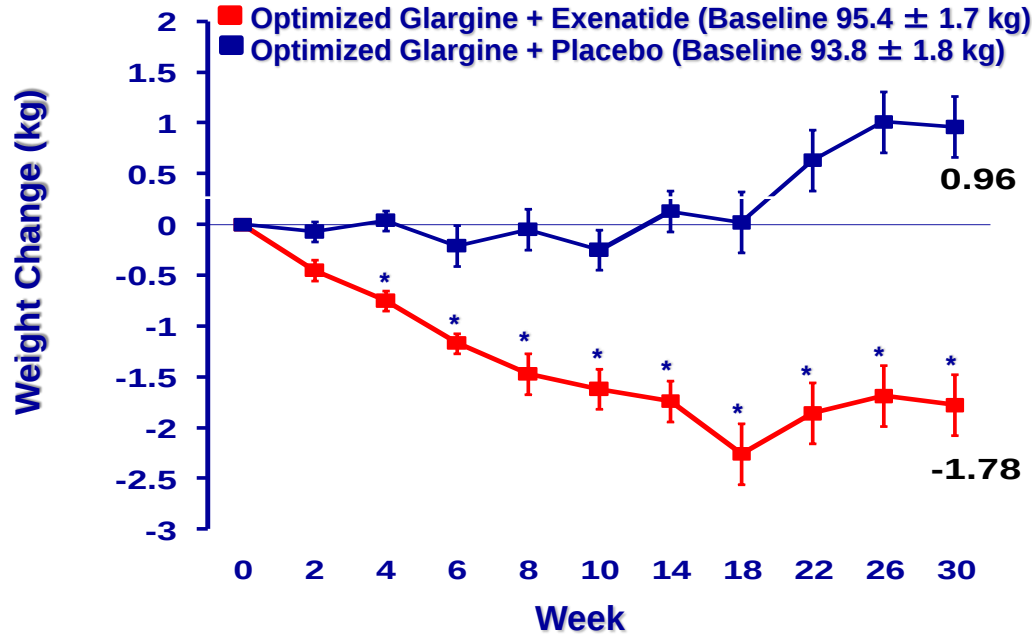
* $p < 0.05$, between treatment comparison.

** $p < 0.001$.

† $p < 0.01$.

Add-On Exenatide to Insulin Glargine-Treated Type 2 Diabetes

Change in Weight From Baseline



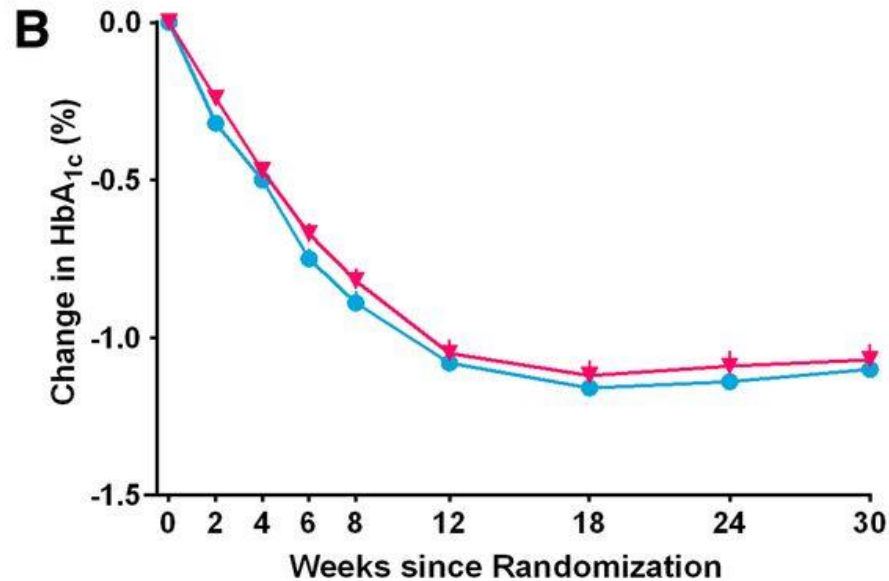
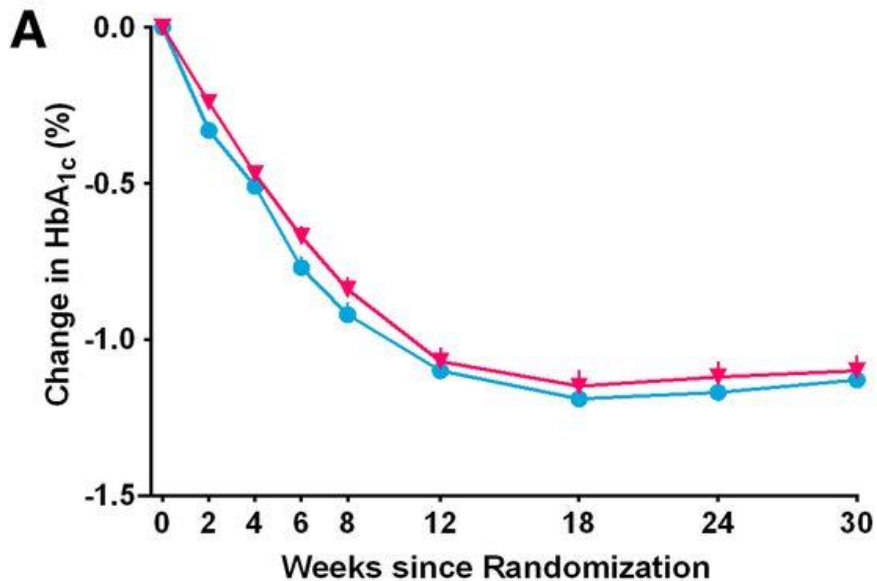
Data presented as LS mean $\pm$ SE.

* $p < 0.001$ between treatment comparison.

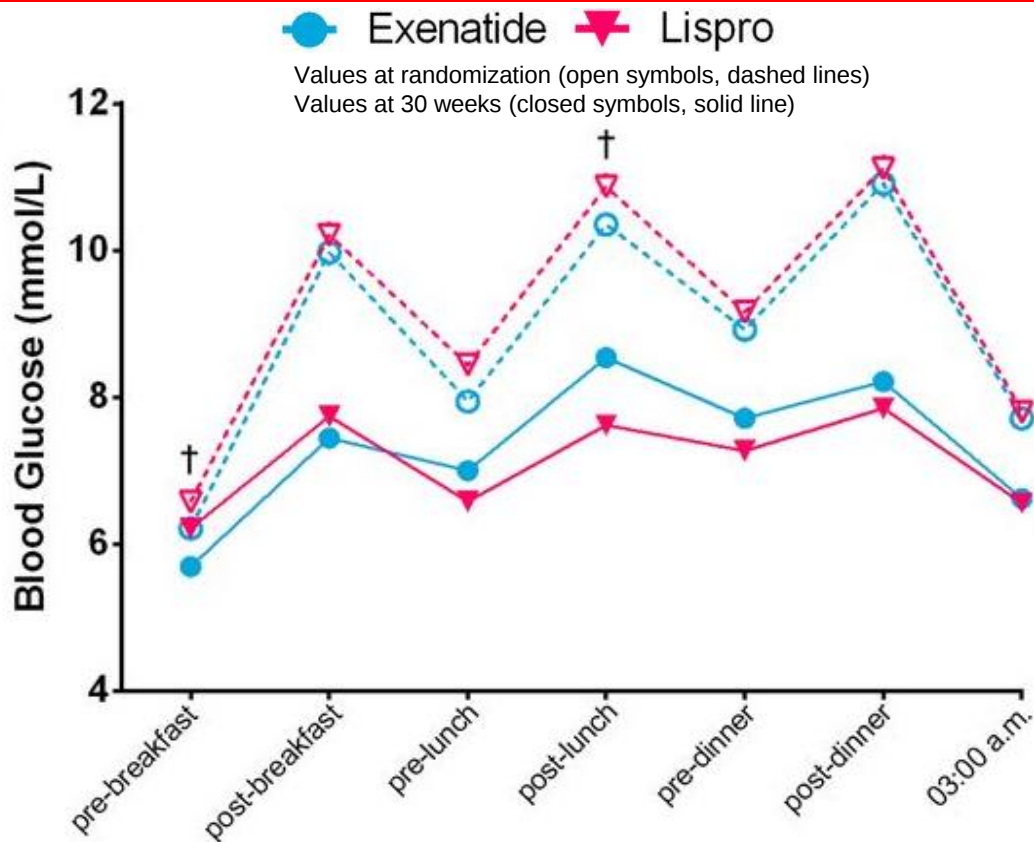
Exenatide or Insulin Lispro with Optimized Basal Insulin

Change in A1c

● Exenatide ▼ Lispro



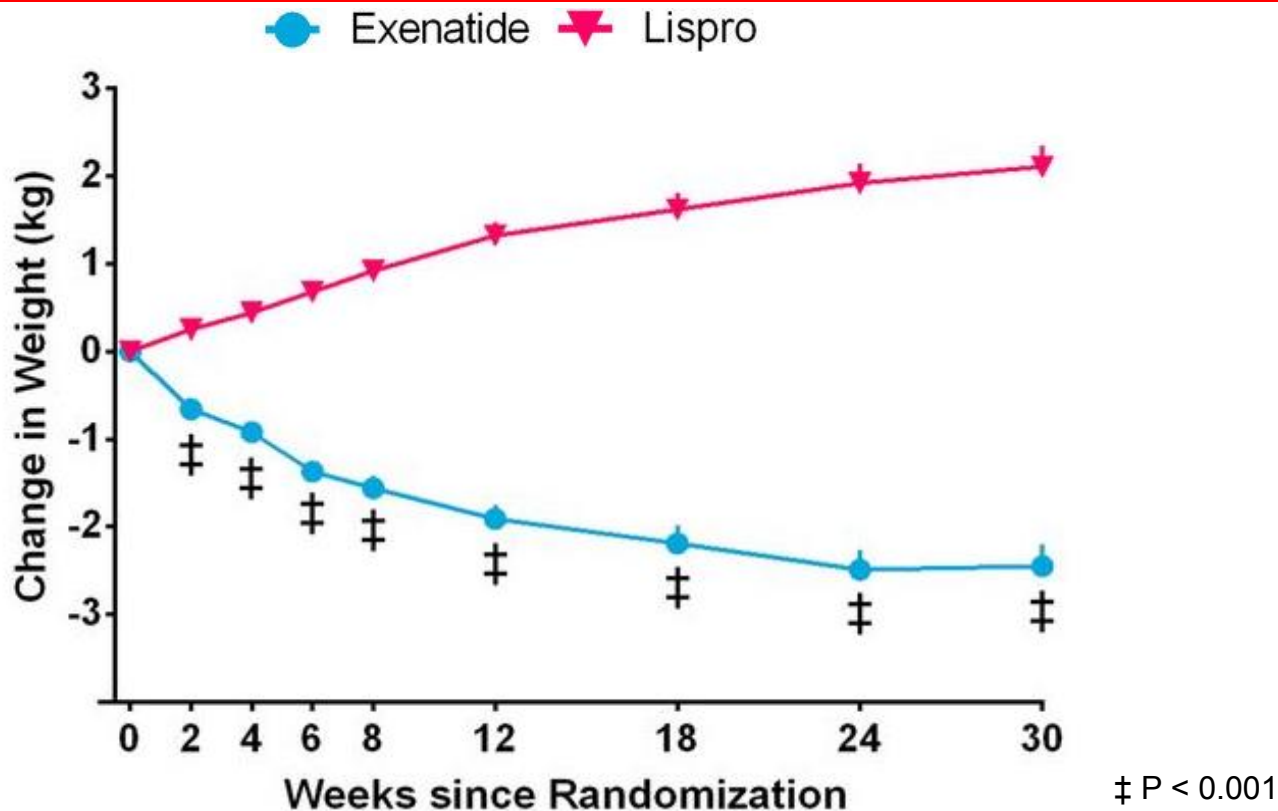
Exenatide or Insulin Lispro with Optimized Basal Insulin Glucose Profile



† P < 0.001, lispro vs. exenatide

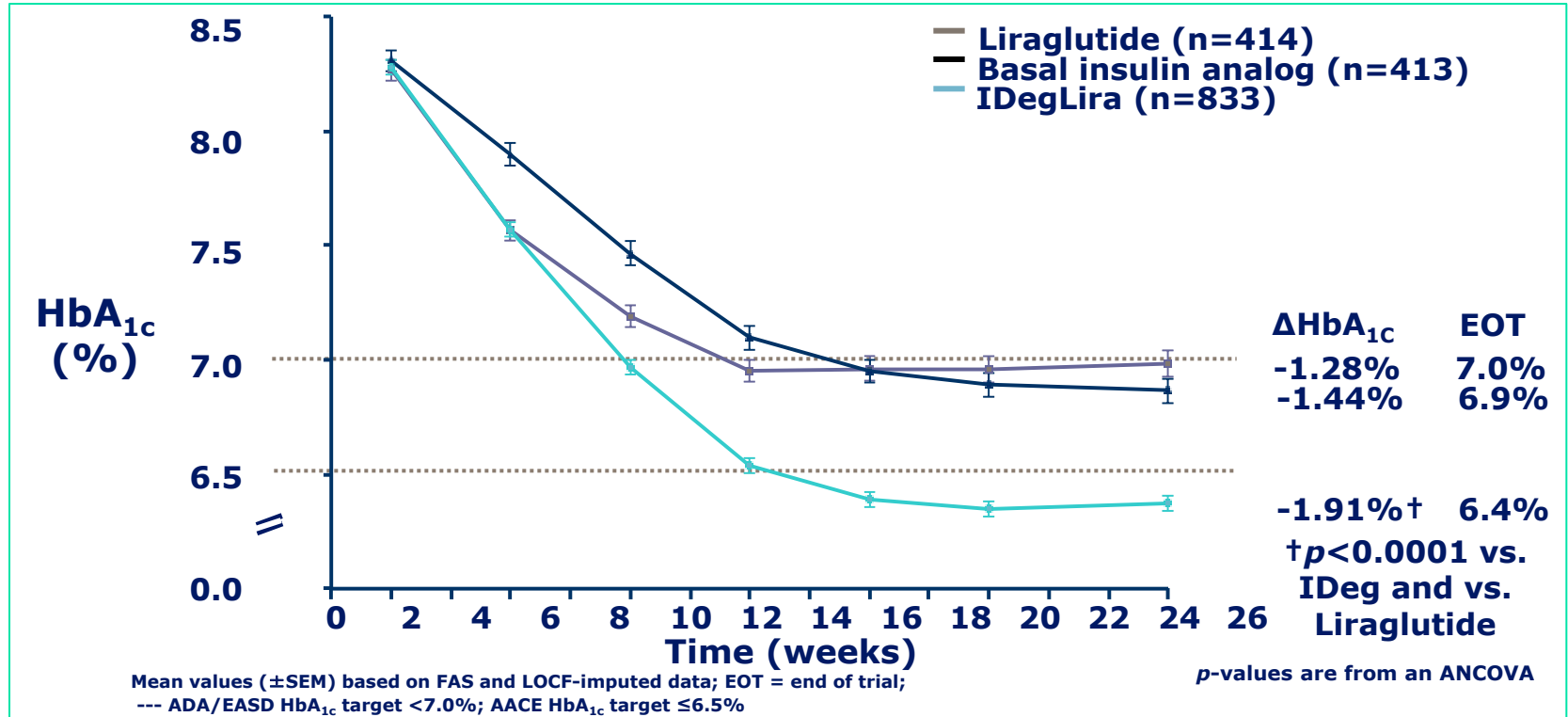
Exenatide or Insulin Lispro with Optimized Basal Insulin

Change in Body Weight



DUAL- I: A1c

Background of Metformin ± Pioglitazone



Degludec vs Liraglutide vs Combination

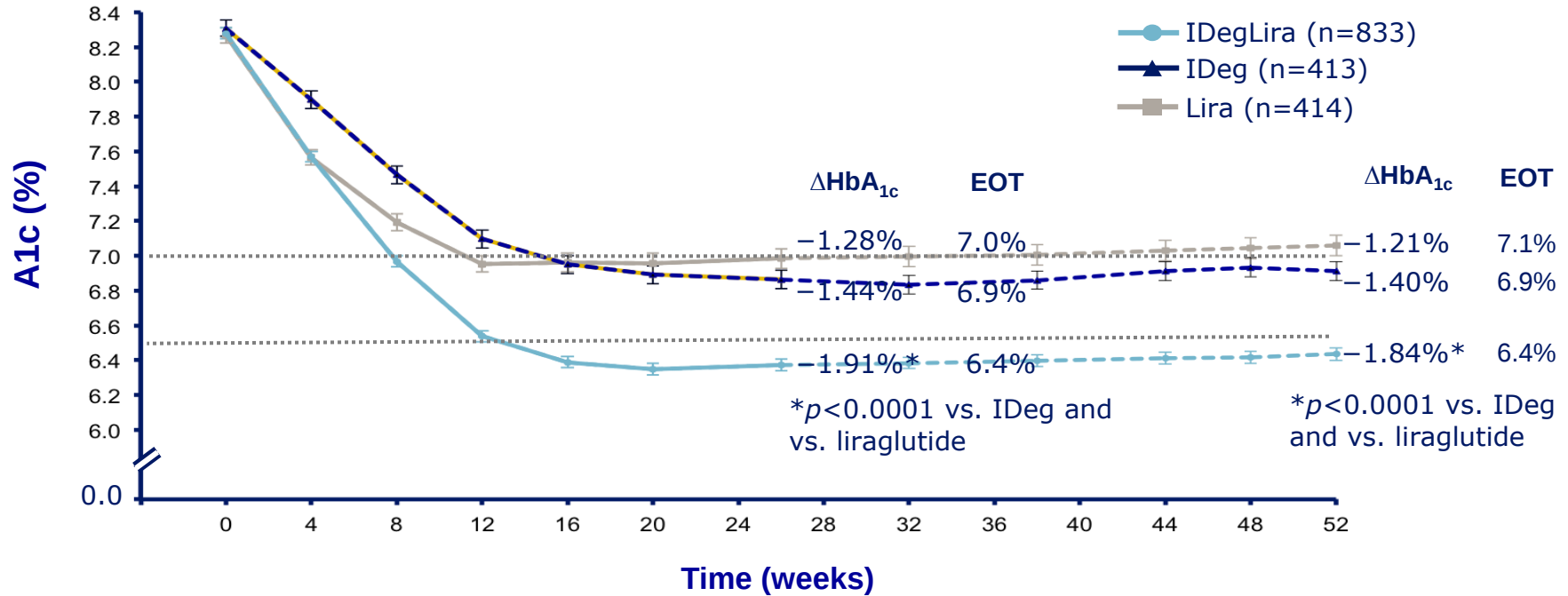
	Degludec	Liraglutide	IDegLira*
Baseline HbA _{1c}	8.3%	8.3%	8.3%
End of trial HbA _{1c}	6.9%	7.0%	6.4%
% reaching HbA _{1c} target of 7%	65%	61%	81%
% reaching HbA _{1c} target of 6.5%	48%	41%	70%
Weight change	+1.5 kg	-3.0 kg	-0.5 kg
Confirmed hypoglycaemia	Low	Very low	Low

*Not FDA approved

 = statistically significant
 = statistically significant

DUAL I Extension

A1c Over Time

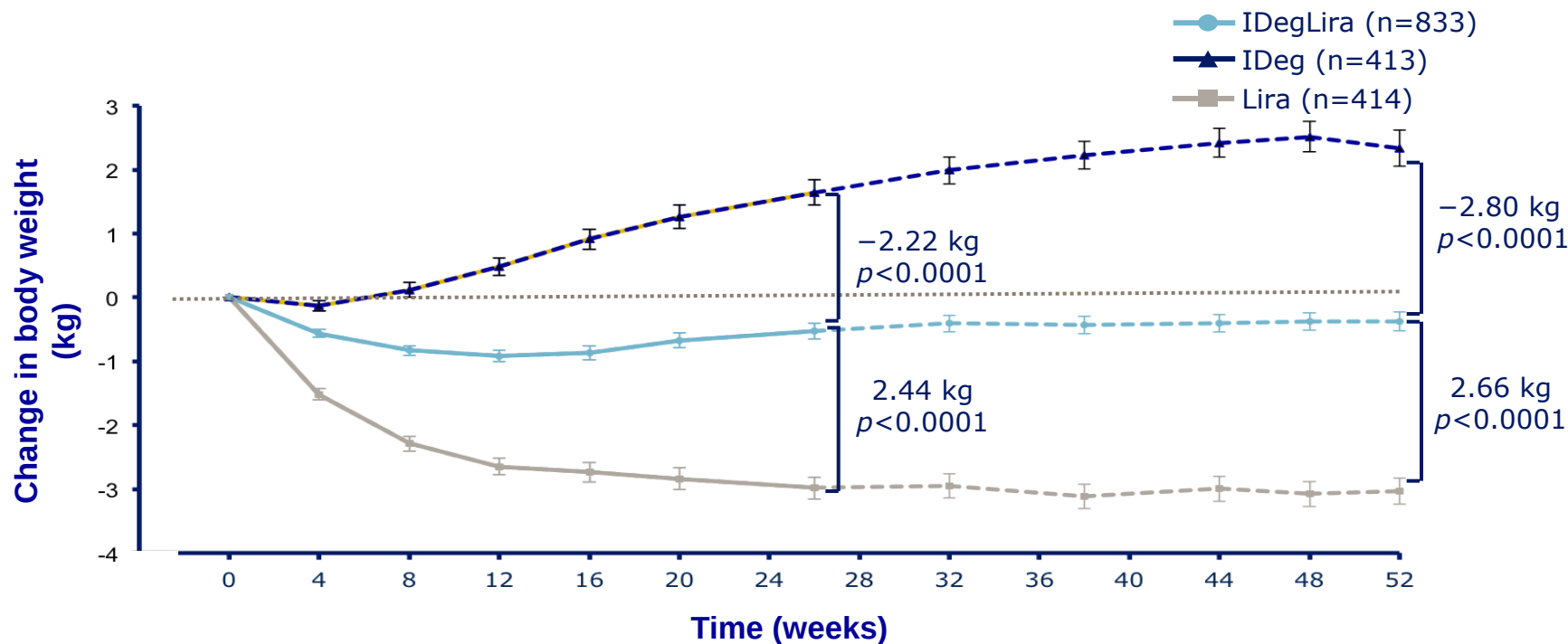


IDegLira not FDA approved

Gough et al. Diabetes 2014;63(Suppl. 1):A17(Abstract #65-OR); Gough et al. Diabetologia 2014;57(Suppl. 1): Abstract 78-OR

DUAL I Extension

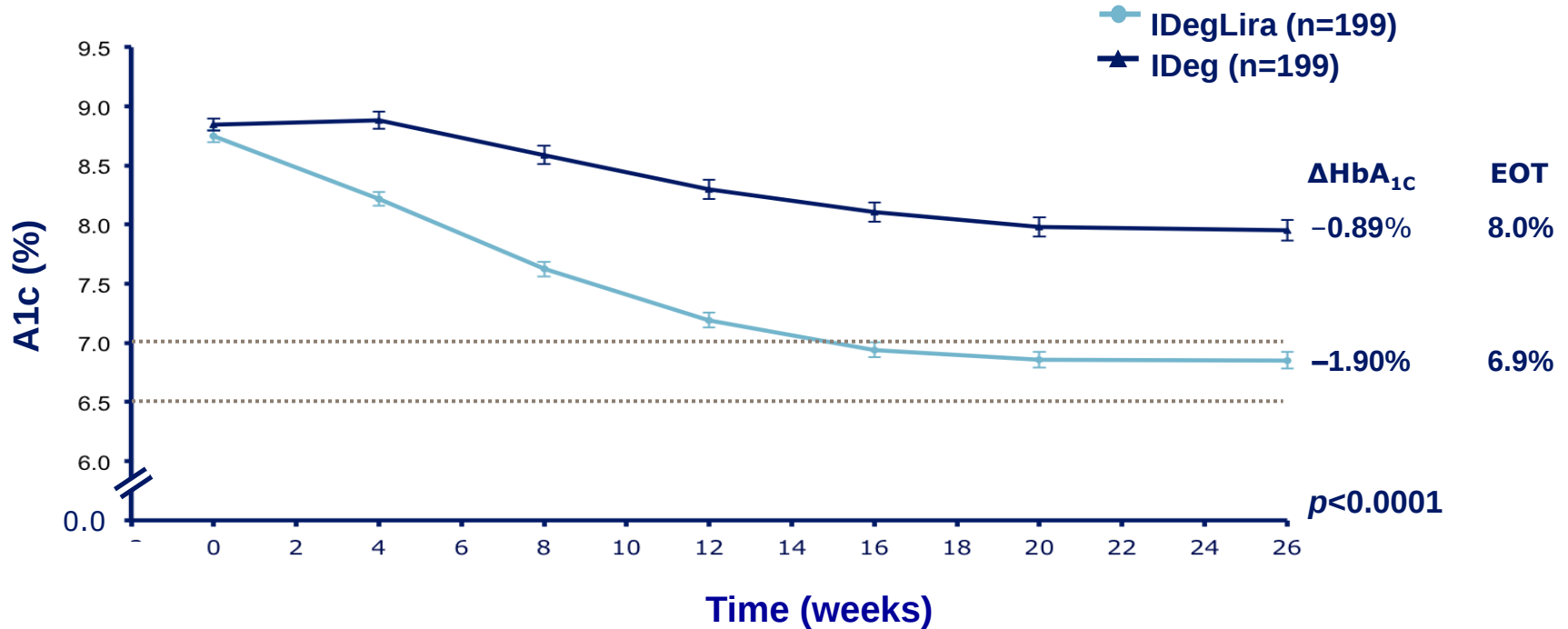
Change in Body Weight Over Time



IDegLira not FDA approved

DUAL II - A1c Over Time

Uncontrolled on Basal Insulin $\pm$ OADs

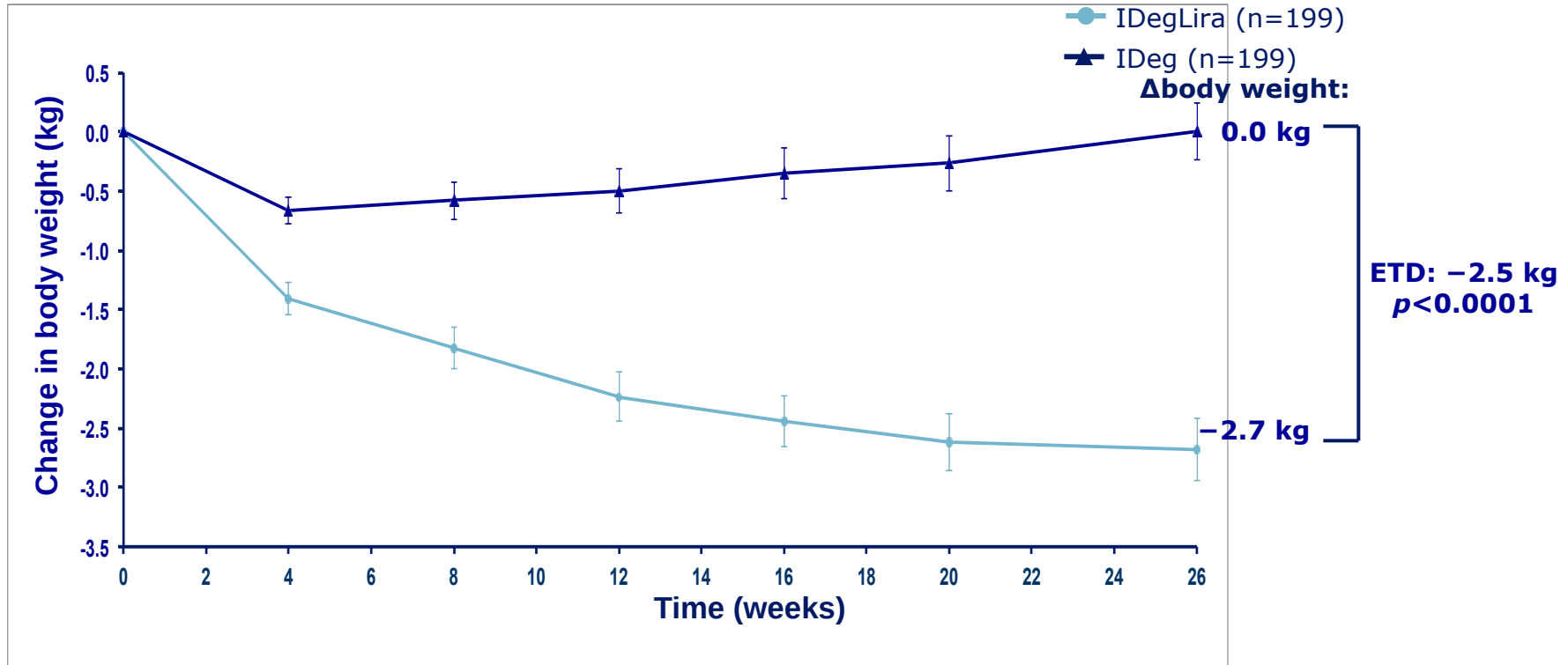


IDegLira not FDA approved

Buse et al. Diabetes Care 2014;37:2926–33

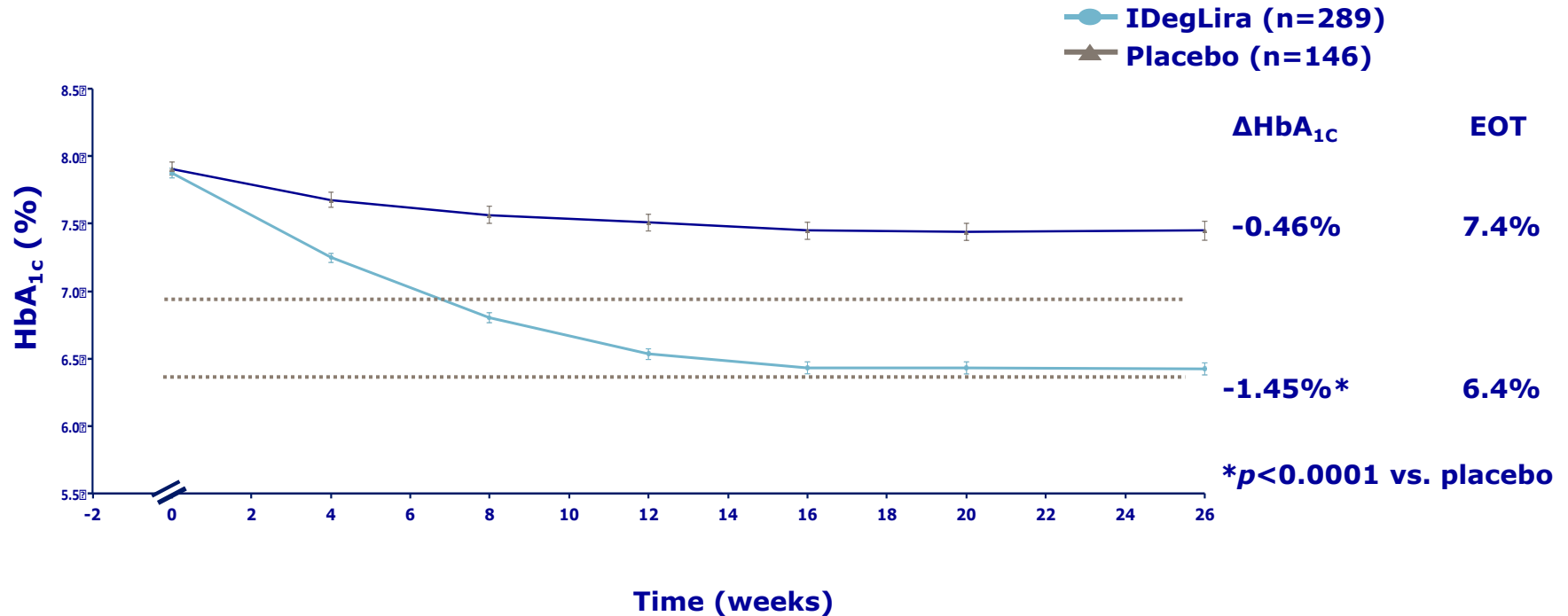
DUAL II

Change in Body Weight Over Time



DUAL IV - A1c Over Time

Background of Sulfonylurea $\pm$ Metformin

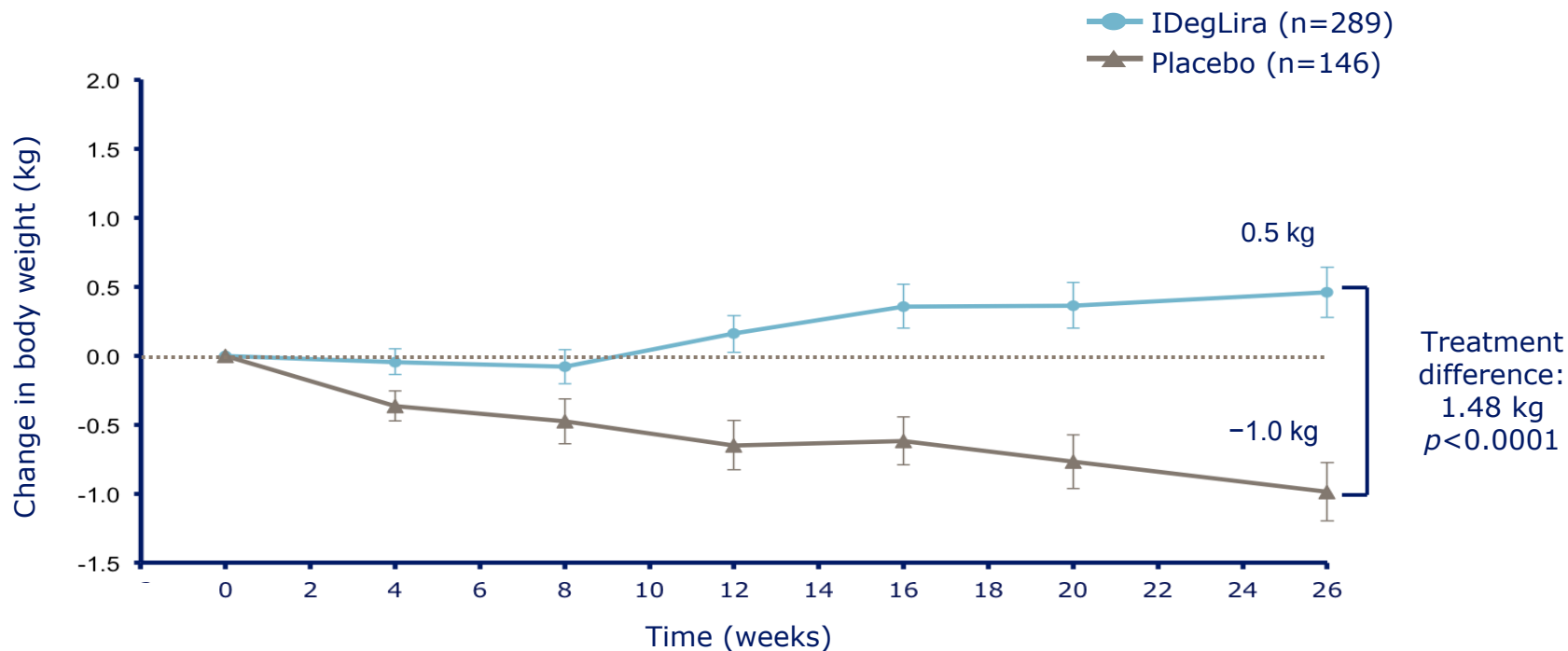


IDegLira not FDA approved

Rodbard et al. [ADA abstract]. Diabetes. 2015; 64(suppl 1):1004-P.

DUAL IV

Change in Body Weight Over Time

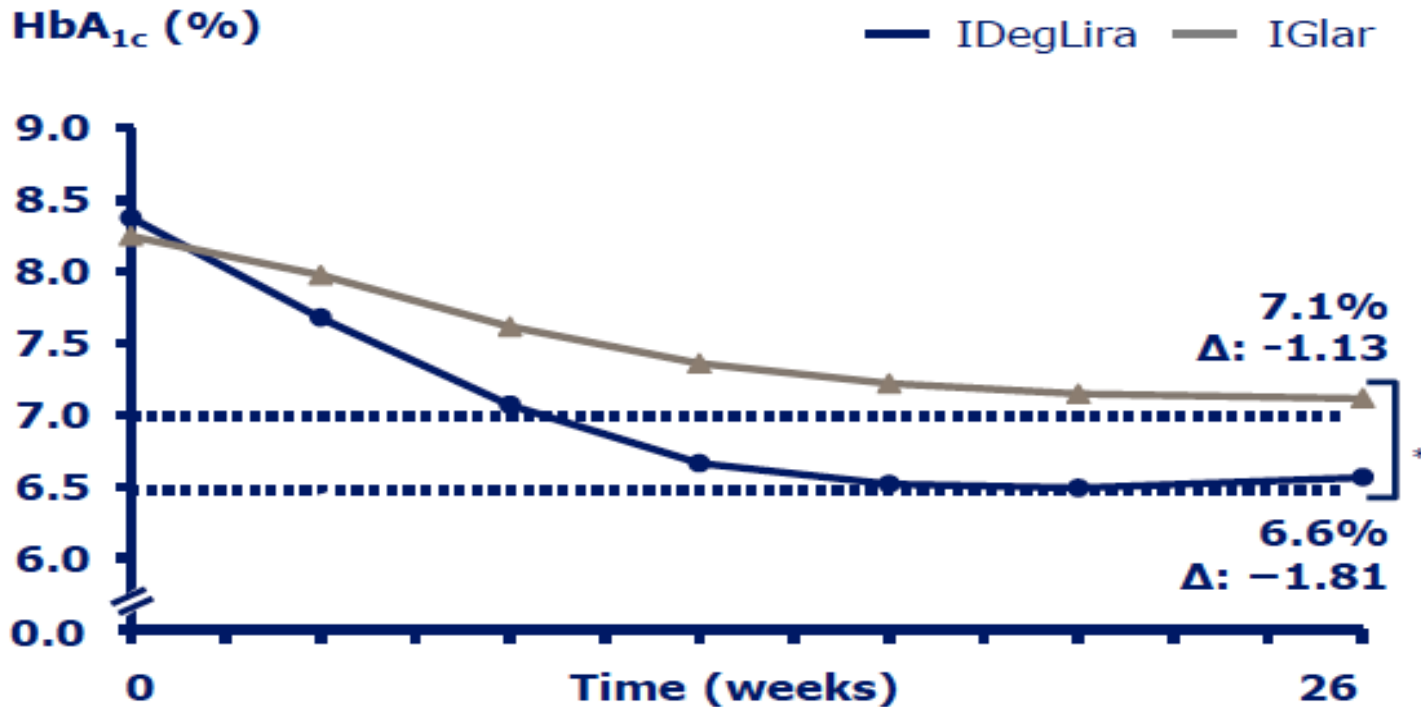


IDegLira not FDA approved

Rodbard et al. [ADA abstract]. Diabetes. 2015; 64(suppl 1):1004-P.

DUAL V - A1c Over Time

IDegLira versus Insulin Glargine

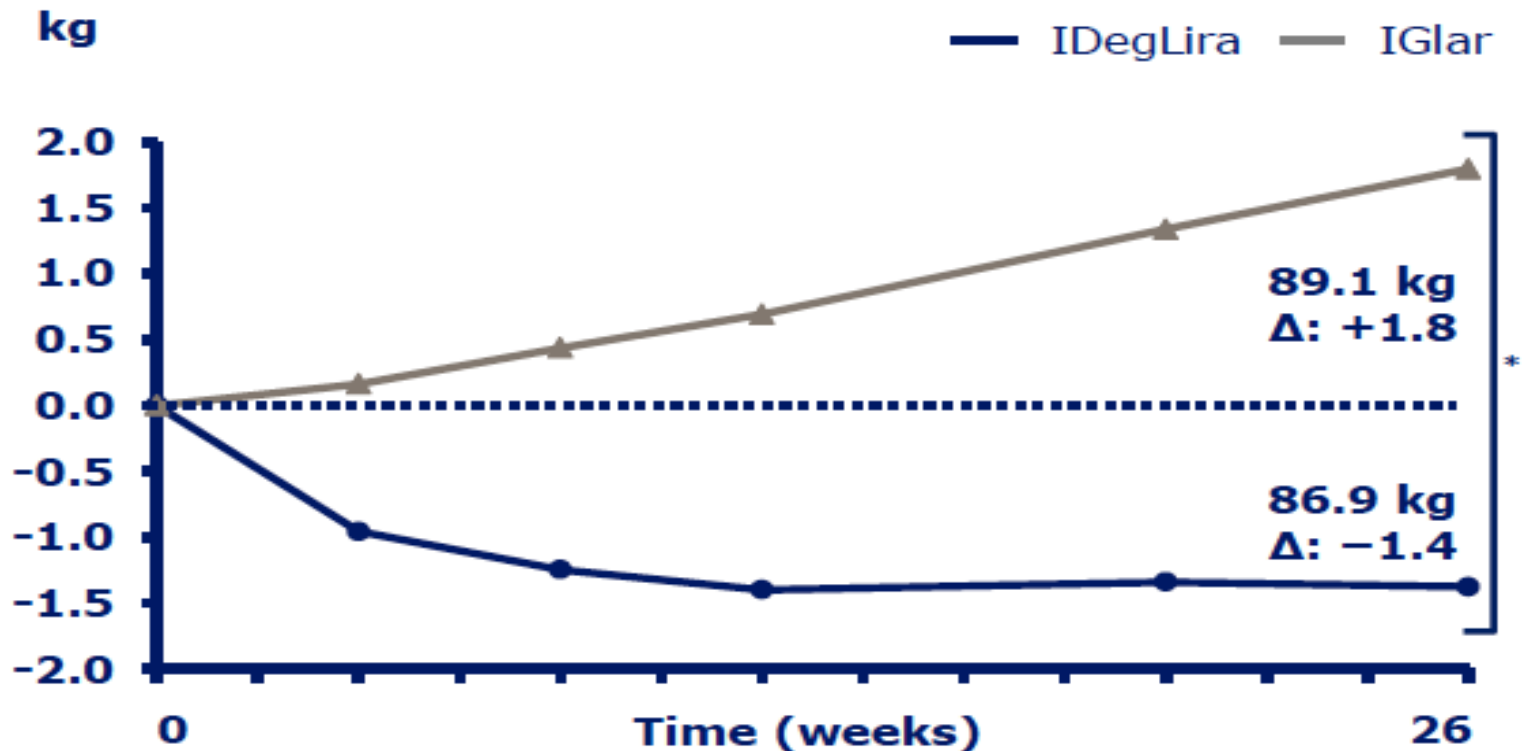


IDegLira not FDA approved

Buse et al. [ADA abstract]. Diabetes. 2015; 64(suppl 1):166-OR.

DUAL V

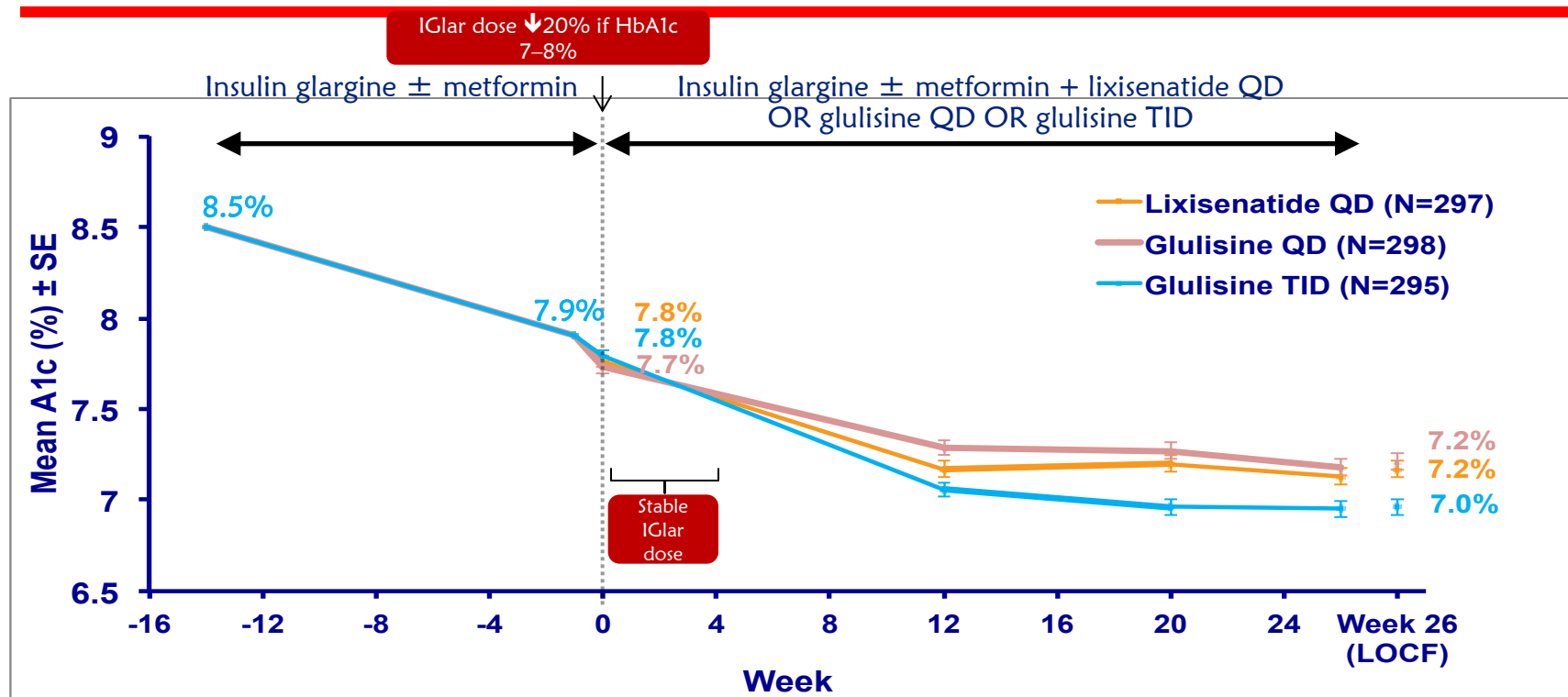
Change in Body Weight Over Time



IDegLira not FDA approved

Buse et al. [ADA abstract]. Diabetes. 2015; 64(suppl 1):166-OR.

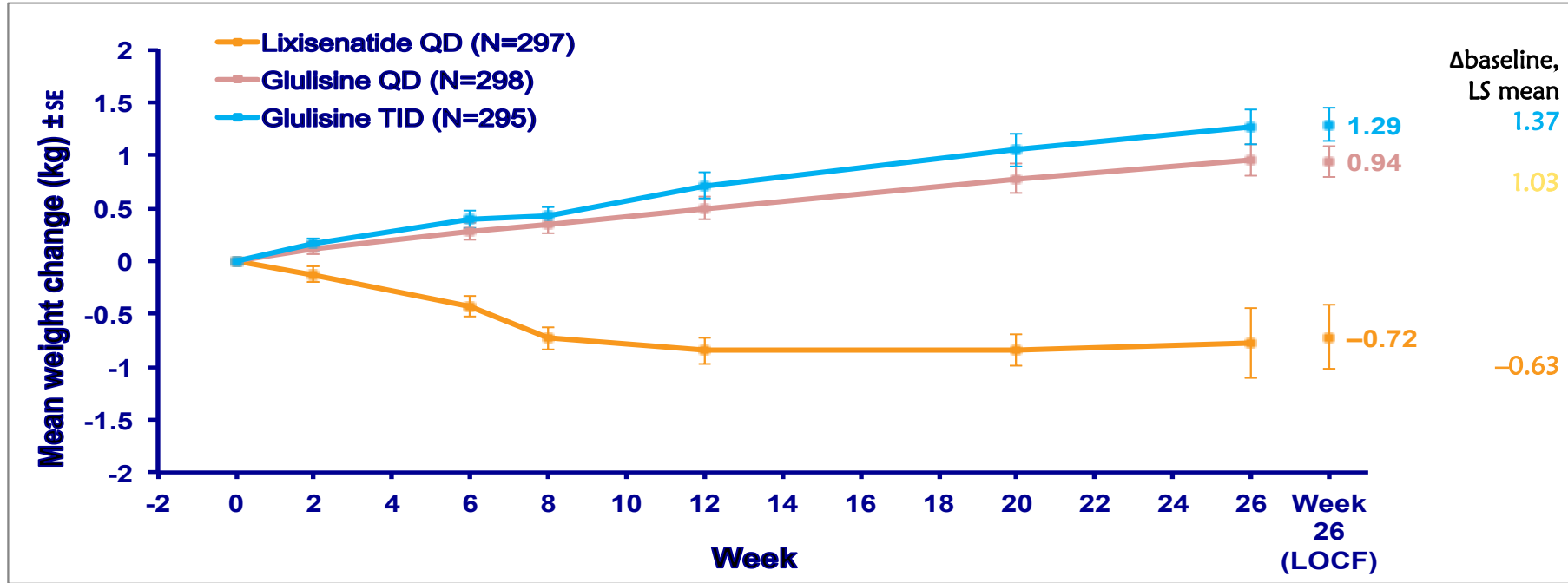
Lixisenatide* + Glargine versus Insulin Glulisine + Glargine



*Not FDA approved

Rosenstock et al. al. Presented at ADA 2015 – Abstract 107-LB.

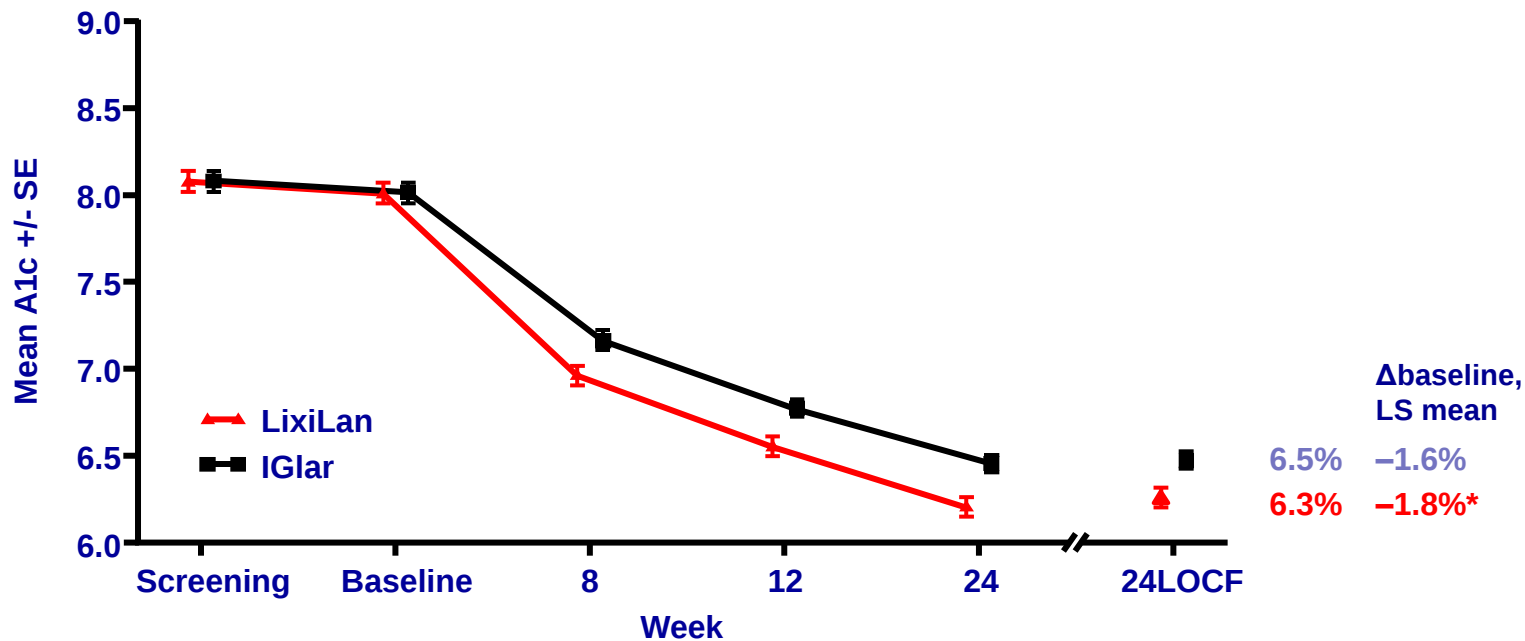
Lixisenatide* + Glargine versus Insulin Glulisine + Glargine



*Not FDA approved

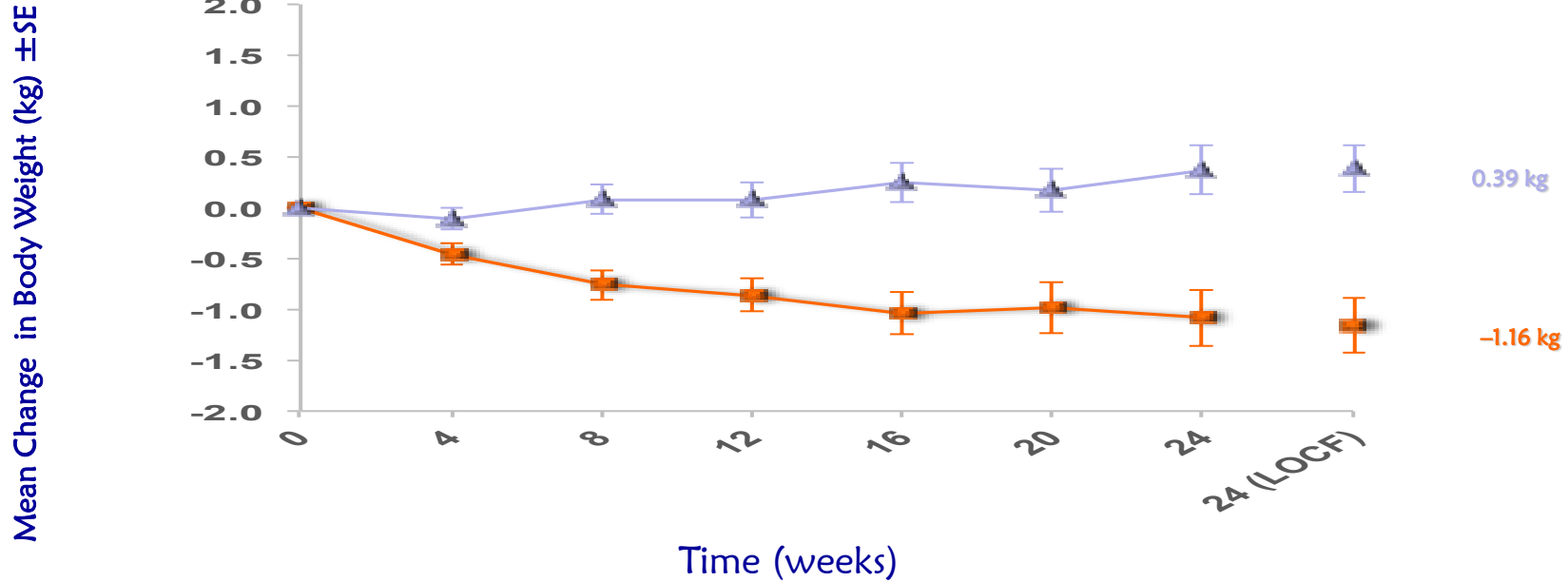
Rosenstock et al. al. Presented at ADA 2015 – Abstract 107-LB.

LixiLan POC: A1c Changes

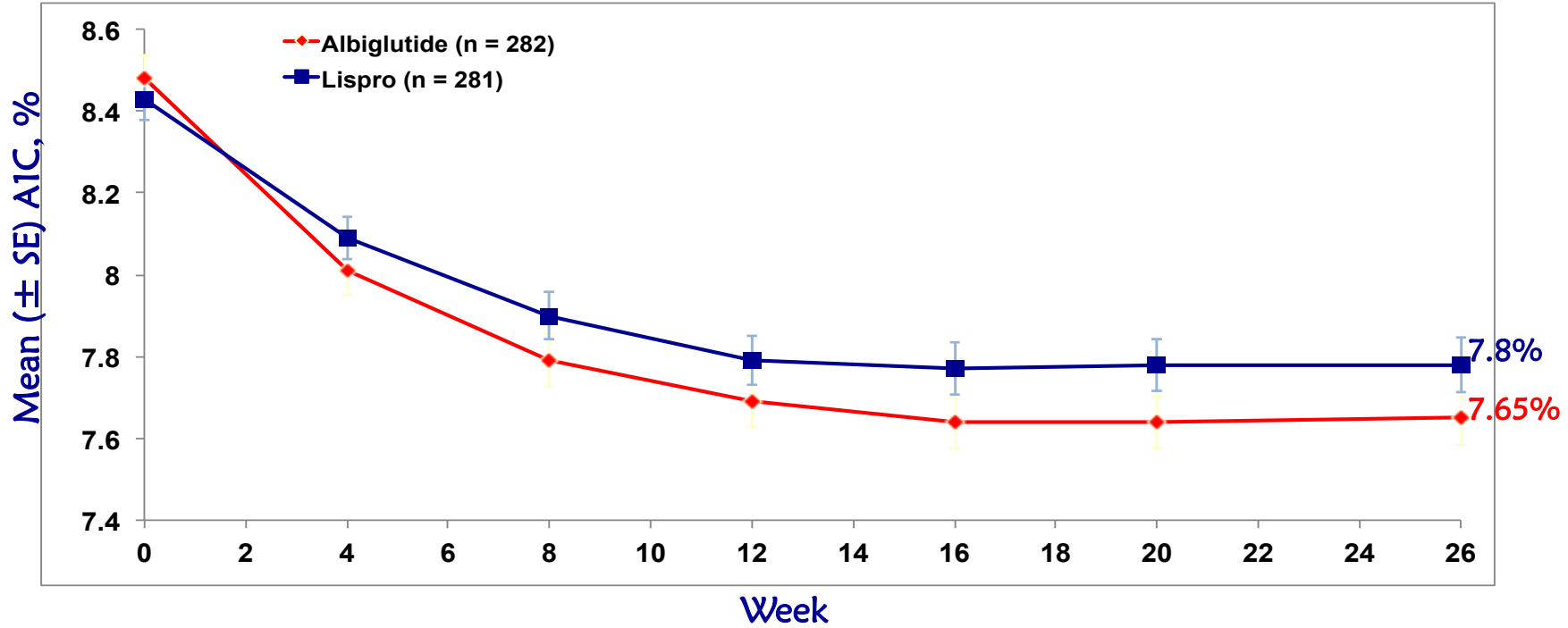


*p = 0.0130

LixiLan POC: Weight Change



Once-Weekly Albiglutide vs Thrice-Daily Lispro Added On to Titrated Glargine + OADs in T2DM



47 IU

Conclusions

- **GLP-1 Receptor Agonists are gaining an increasingly important role in diabetes management**
- **GLP-1 RAs in development include monthly formulations and an implanted system that lasts 6-12 months**
- **Preparations combining insulin with GLP-1 RAs have much potential promise**