Oral Glucose Lowering With Linagliptin Plus Metformin is a Viable Initial Treatment Strategy in Patients With Newly Diagnosed Type 2 Diabetes and Marked Hyperglycemia

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Disclosures
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Introduction

- Early and aggressive management of hyperglycemia in patients newly diagnosed with type 2 diabetes (T2DM) improves long-term clinical outcomes[1,2]
- Insulin treatment often advocated for marked hyperglycemia[3-5] but poses challenges for some newly diagnosed patients and physicians[6]
- Oral combination therapy may be an attractive alternative,[3-5] but scarcity of data from clinical trials in newly diagnosed patients with marked hyperglycemia
- Combining metformin – the usual first-line agent – with a dipeptidyl peptidase (DPP)-4 inhibitor of interest due to complementary mechanisms of action and low intrinsic risk of hypoglycemia, the main factor limiting insulin treatment

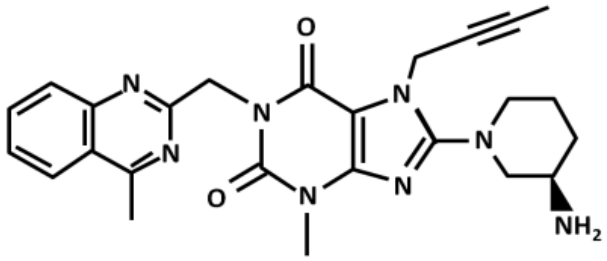
1. UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:837-853; 2. Holman R, et al. *N Engl J Med*. 2008;359:1577-1589; 3. Inzucchi S, et al. *Diabetes Care*. 2012;35:1364-1379; 4. Garber A, et al. *Endocr Pract*. 2013;19:327-336; 5. Harper W, et al. *Can J Diabetes*. 2013;37:S61-S68; 6 Ross S, et al. *Curr Med Res Opin*. 2011;27 Suppl 3:13-20

Linagliptin characteristics

Linagliptin:

Non-peptidomimetic DPP-4 inhibitor

Directly binds to the active site of the DPP-4 enzyme



- DPP-4 inhibitor with a unique xanthine-based structure[1]
- Mainly excreted unchanged via bile and gut[1,2]
- Once-daily dosing and no dose adjustment for all patients, including those with renal or hepatic impairment[2]
- Overall safety profile similar to placebo (no weight gain, low risk of hypoglycemia)[2,3]

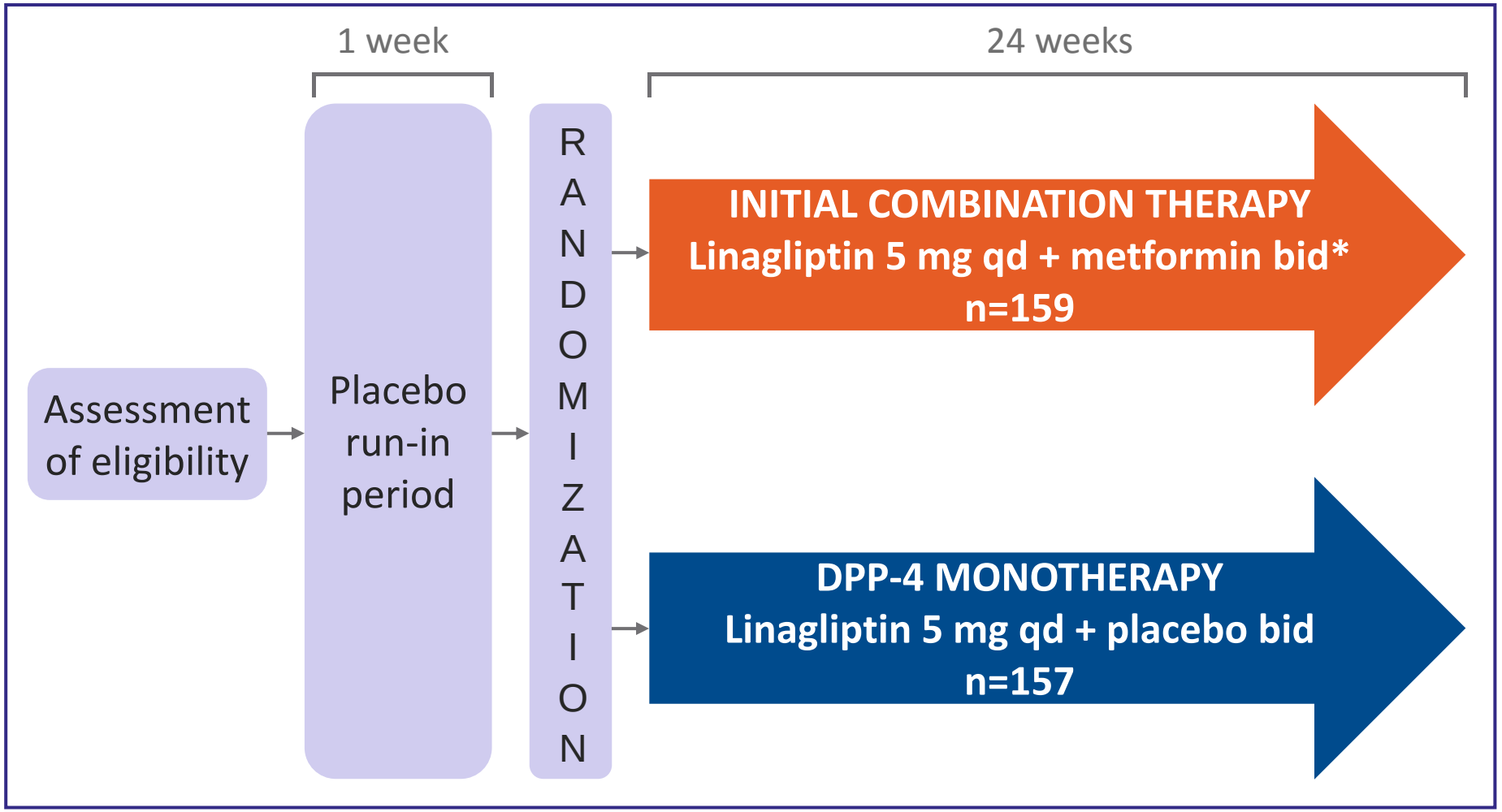
1. Deacon C and Holst J. *Expert Opin Investig Drugs*. 2010;19:133-140; 2. Tradjenta (linagliptin) prescribing information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc., 2013; Scott L. *Drugs Ther Perspect*. 2012;28:1-5

Objective

- Recent 24-week randomized study in newly diagnosed T2DM patients with marked hyperglycemia (mean HbA1c 9.8%)[1]
- We present here a prespecified analysis of this study to examine clinically relevant subgroups:
  - baseline HbA1c
  - age
  - body-mass index
  - kidney function
  - race
  - ethnicity

1. Ross SA, et al. P-1104. International Diabetes Federation - 22nd World Diabetes Congress, 2013

Study design



Registered with ClinicalTrials.gov, NCT01512979

*Metformin was initiated at 1000 mg/day (500 mg bid) and was up-titrated in the first 6 weeks to 1500 mg/day (500 mg bid + 500 mg qd) or to a maximal dose of 2000 mg/day (1000 mg bid) if fasting plasma glucose was >110 mg/dL (6.1 mmol/L) and depending on tolerability. Titration was conducted under double-blind conditions

Baseline characteristics

	Linagliptin + metformin	Linagliptin
Age, years	49.0 ± 10.9	48.6 ± 11.2
Male, n (%)	69 (43.4)	77 (49.0)
Race, n (%)		
White	97 (61.0)	85 (54.1)
Asian	57 (35.8)	64 (40.8)
Black	5 (3.1)	6 (3.8)
Native American/Alaskan	0	2 (1.3)
Diabetes duration <1 year, n (%)	159 (100)	155 (98.7)*
No prior antidiabetes drugs, n (%)	159 (100)	157 (100)
HbA1c, % (mmol/mol)†	9.8 ± 1.2 (83 ± 13)	9.9 ± 1.1 (84 ± 12)
Fasting plasma glucose, mg/dL†	196 ± 54	198 ± 61
Body-mass index, kg/m^2	29.8 ± 5.8	29.6 ± 5.4
Macrovascular disease, n (%)	67 (42.1)	72 (45.9)
Microvascular disease, n (%)	20 (12.6)	18 (11.5)

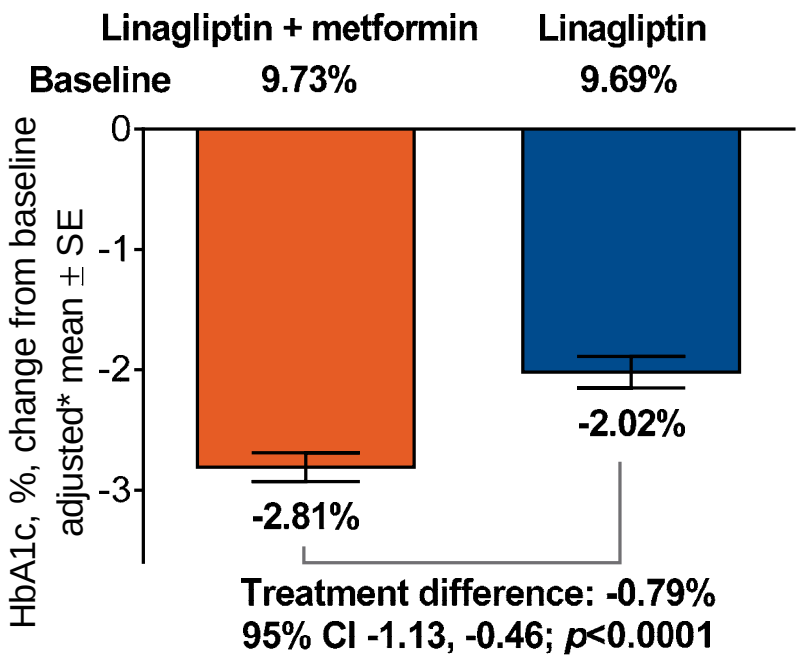
Data are mean ± SD for the treated set of patients (linagliptin and metformin: n=159; linagliptin: n=157) unless otherwise noted

*For two linagliptin patients, the time since diagnosis of T2DM was ≥12 months at screening

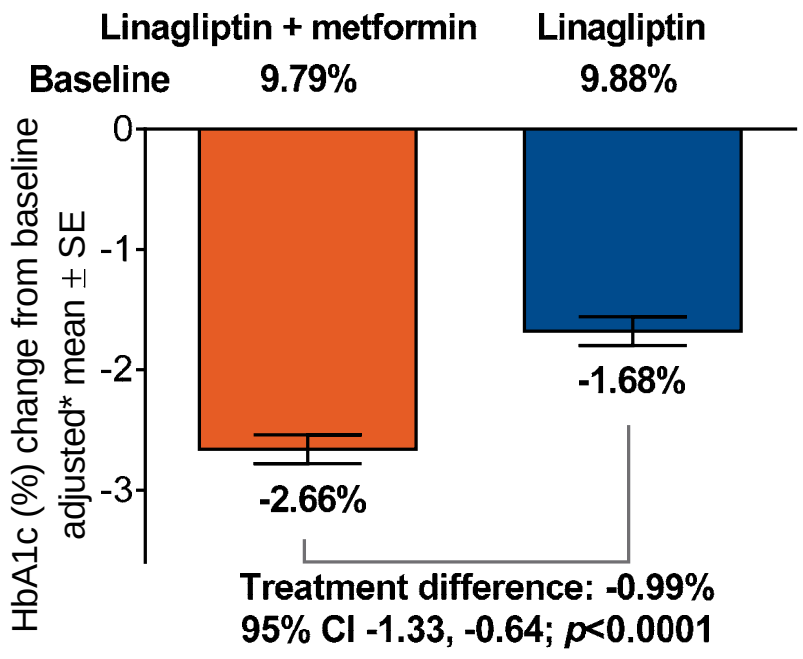
†Full-analysis set (linagliptin and metformin: n=153; linagliptin: n=150)

Change in HbA1c at Week 24 (primary endpoint) in overall population

Per-protocol completers cohort (PPCC)

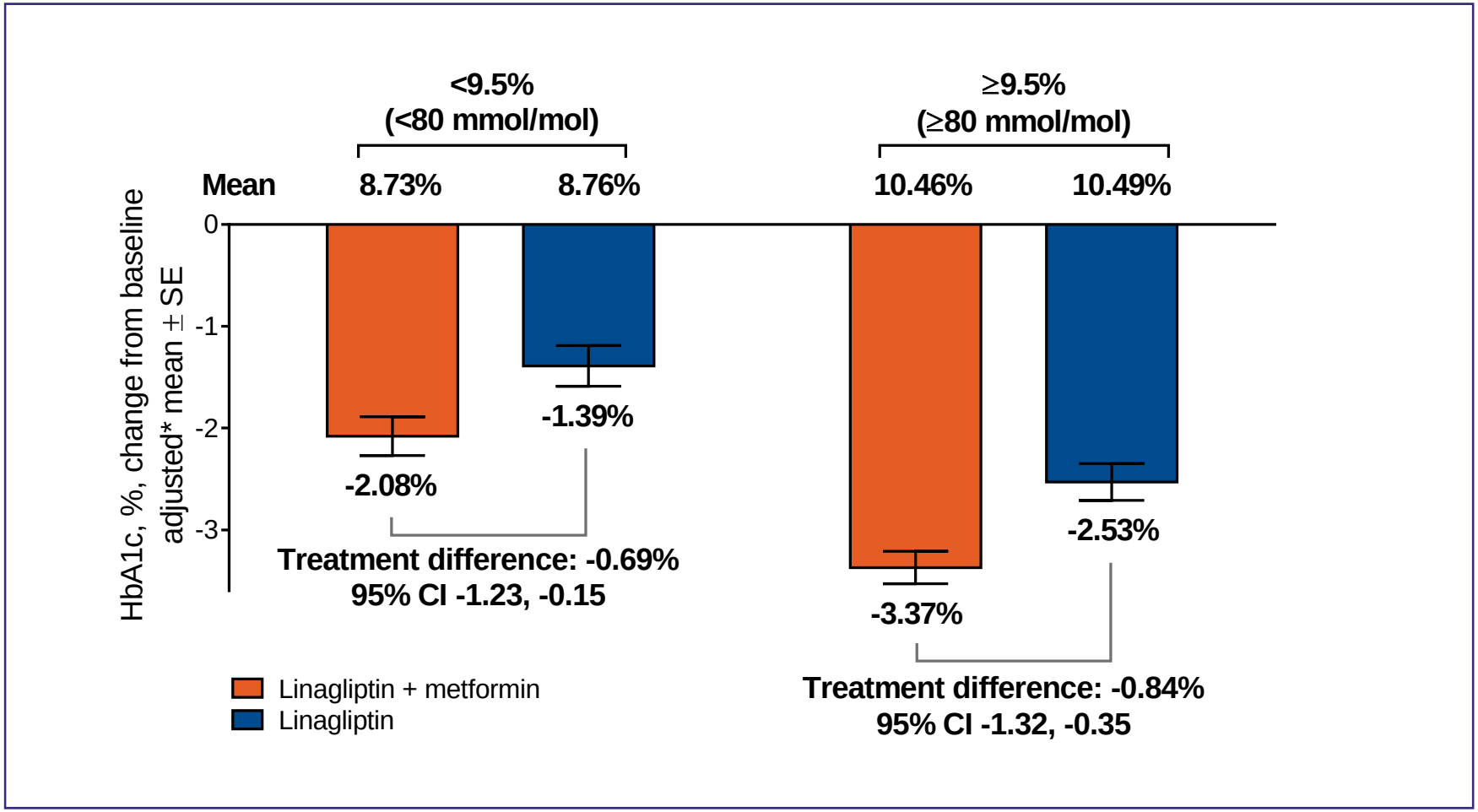


Full-analysis set (LOCF)



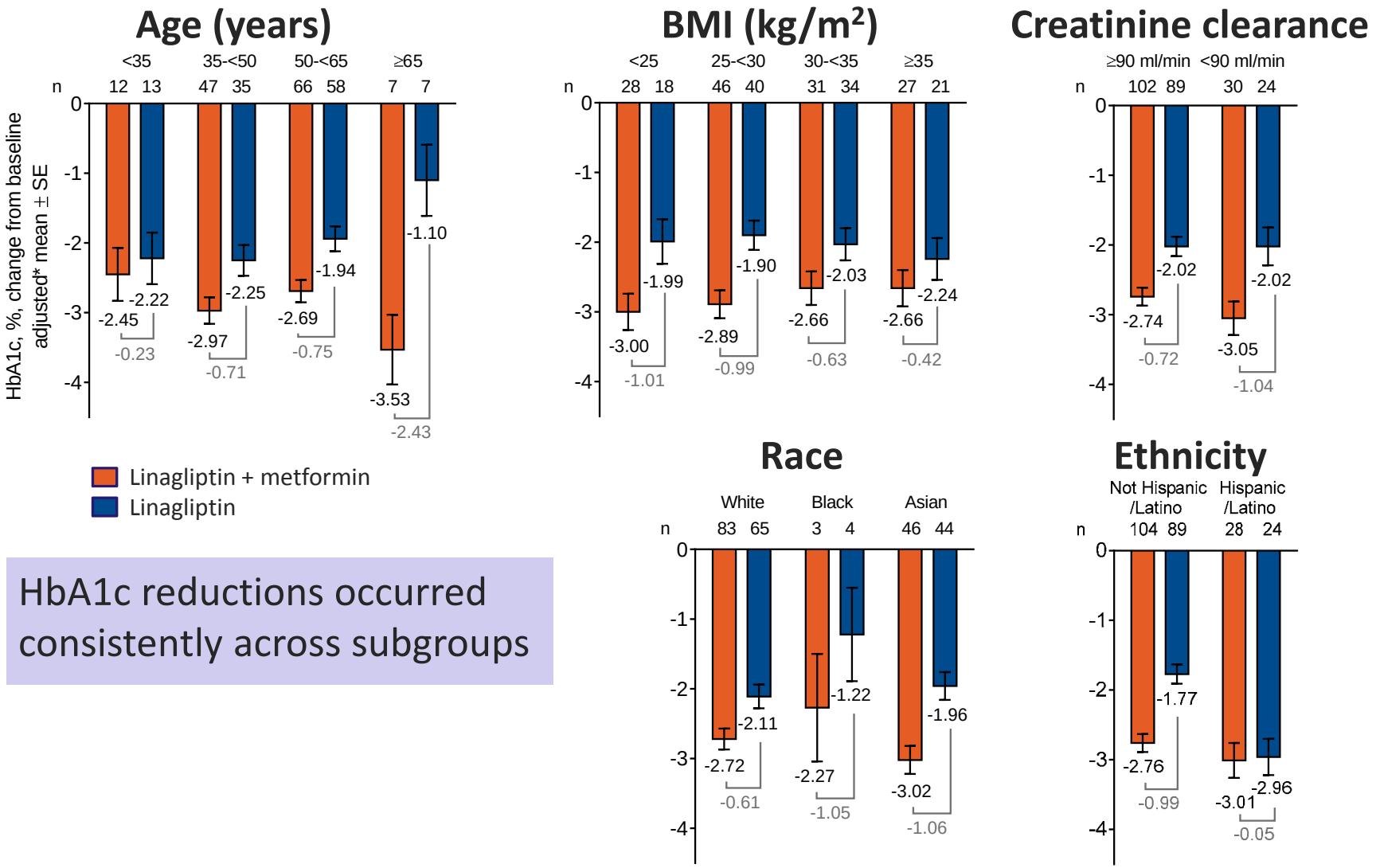
Per-protocol completers cohort is all randomized patients who received ≥1 dose of study drug, had a baseline HbA1c measurement, had no important protocol violations, completed 24 weeks of treatment without receiving glycemic rescue, and had an HbA1c measurement at Week 24. Full-analysis set approximates the intention-to-treat set and comprises all randomized patients who received ≥1 dose of study drug, had a baseline HbA1c measurement and 1 on-treatment HbA1c measurement.
*Analysis of covariance model includes continuous baseline HbA1c and treatment. LOCF = last observation carried forward

Change in HbA1c at Week 24 by baseline HbA1c <9.5/≥9.5%: PPCC



*Analysis of covariance model includes categorical baseline HbA1c, treatment and treatment by categorical baseline HbA1c interaction. PPCC = per-protocol completers cohort: all randomized patients who received ≥1 dose of study drug, had a baseline HbA1c measurement, had no important protocol violations, completed 24 weeks of treatment without receiving glycemic rescue, and had an HbA1c measurement at Week 24

Change in HbA1c at Week 24 in demographic subgroups



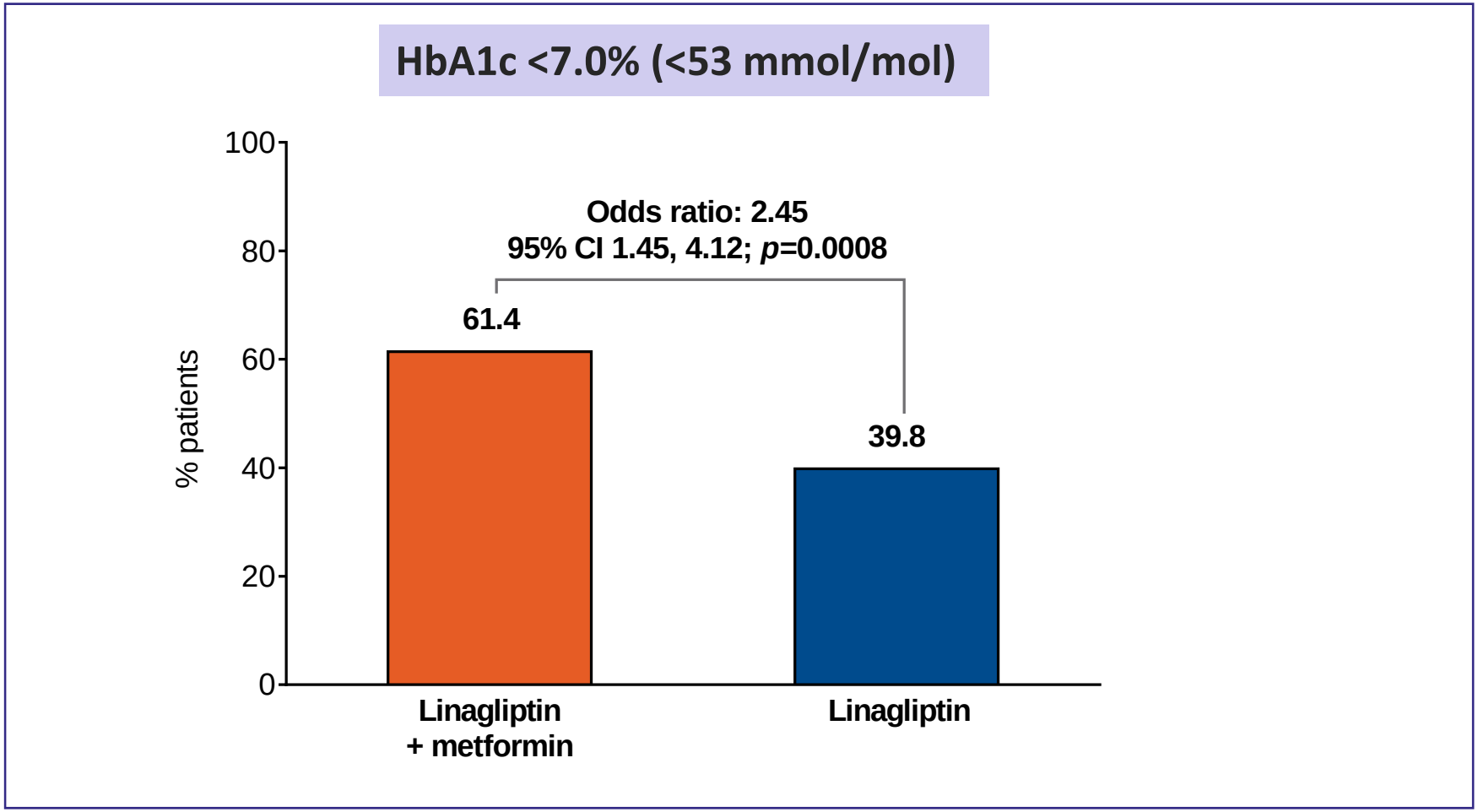
HbA1c reductions occurred consistently across subgroups

Data are for the PPCC. Creatinine clearance was estimated by the Cockcroft-Gault equation

*Analysis of covariance model includes continuous baseline HbA1c, treatment, subgroup, and treatment by subgroup interaction

BMI = body-mass index; PPCC = per-protocol completers cohort: all randomized patients who received ≥1 dose of study drug, had a baseline HbA1c measurement, had no important protocol violations, completed 24 weeks of treatment without receiving glycemic rescue, and had an HbA1c measurement at Week 24

Target HbA1c (<7%) response rate at Week 24



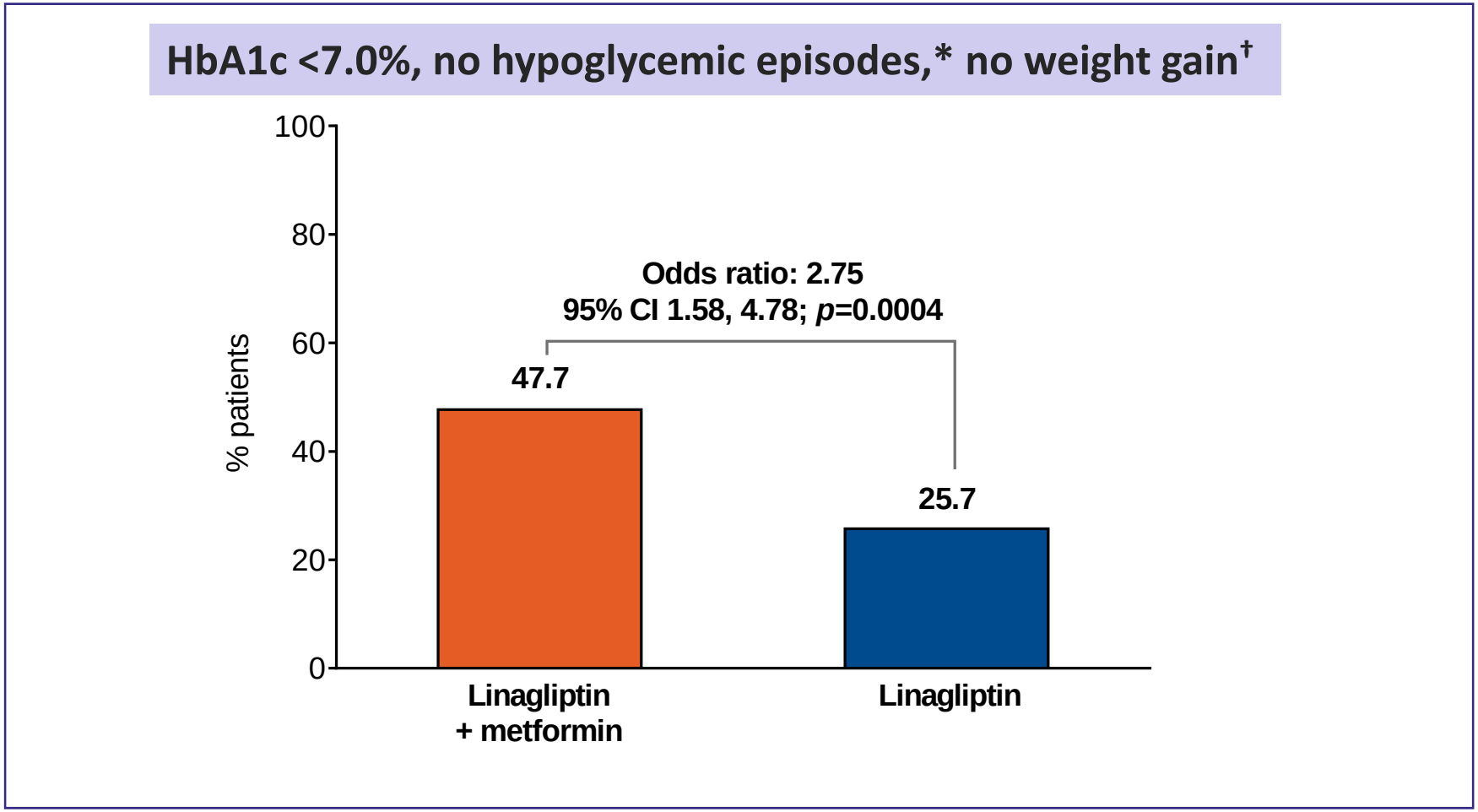
Data are for the PPCC (NCF) from logistic regression model with continuous baseline HbA1c and treatment. NCF = non-completers considered failures; PPCC = per-protocol completers cohort: all randomized patients who received ≥1 dose of study drug, had a baseline HbA1c measurement, had no important protocol violations, completed 24 weeks of treatment without receiving glycemic rescue, and had an HbA1c measurement at Week 24

Adverse events in the overall population (treated set)

Patients, %	Linagliptin + metformin (n=159)	Linagliptin (n=157)
Any AE	56.0	61.1
Drug-related AE	8.8	5.7
AE leading to discontinuation	1.3	1.3
Serious AE	1.9	1.3
Death	0.0	0.0
Requiring hospitalization	1.9	1.3
Drug-related	0.0	0.0
Hypoglycemia	1.9	3.2
AE of special interest*	3.1	3.8
Gastrointestinal disorders†	14.5	13.4

Treated set: all randomized patients who received ≥1 dose of study medication
*Pancreatitis, renal AE, hepatic AE, hypersensitivity reaction, severe cutaneous reaction
†System organ class from the Medical Dictionary for Regulatory Activities, version 16.0
AE = adverse event

Achievement of composite endpoint at Week 24



Data are from post-hoc analysis of the PPCC (NCF) using logistic regression model including baseline HbA1c and treatment. *Investigator-reported hypoglycemia. †Weight gain defined as a change in body weight from baseline of >1 kg. NCF = non-completers considered failures; PPCC = per-protocol completers cohort: all randomized patients who received ≥1 dose of study drug, had a baseline HbA1c measurement, had no important protocol violations, completed 24 weeks of treatment without receiving glycemic rescue, and had an HbA1c measurement at Week 24

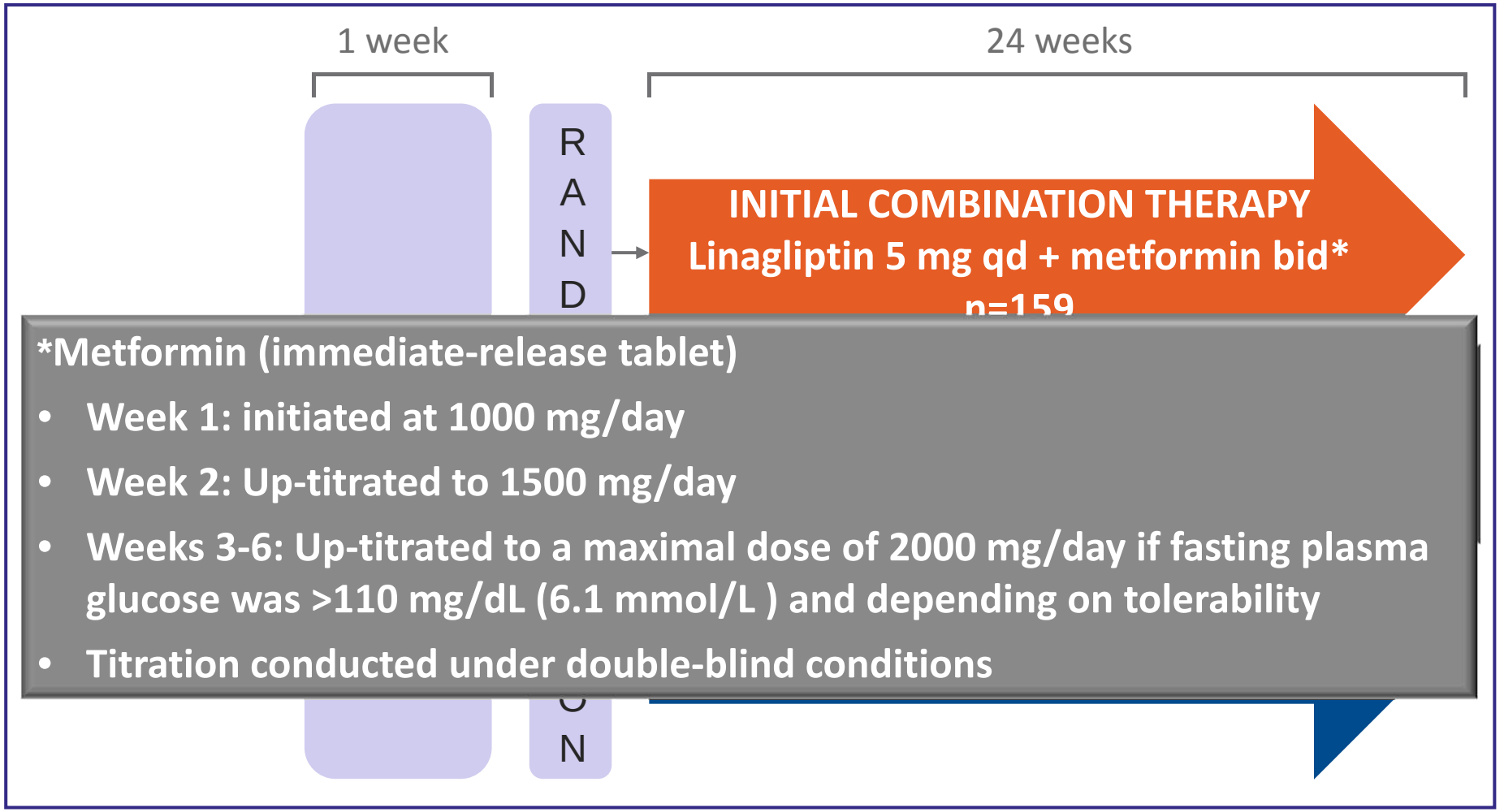
Conclusions

- Linagliptin + metformin combination led to consistent HbA1c reductions (~60% at target) across clinically relevant patient subgroups in newly diagnosed T2DM patients with marked hyperglycemia
  - clinically relevant response also with linagliptin monotherapy in a sizable percentage of patients (~40% at target)
- Very low incidence of hypoglycemia and no weight gain
- Successful early combination of metformin + DPP-4 inhibition in T2DM patients even with marked hyperglycemia
- No safety concerns
  - Long-term safety of metformin + linagliptin being studied in CAROLINA®, the only large cardiovascular outcomes study of a DPP-4 inhibitor actively comparing long-term drug safety versus a sulfonlyurea (glimepiride)[1]

[1]ClinicalTrials.gov; NCT01243424

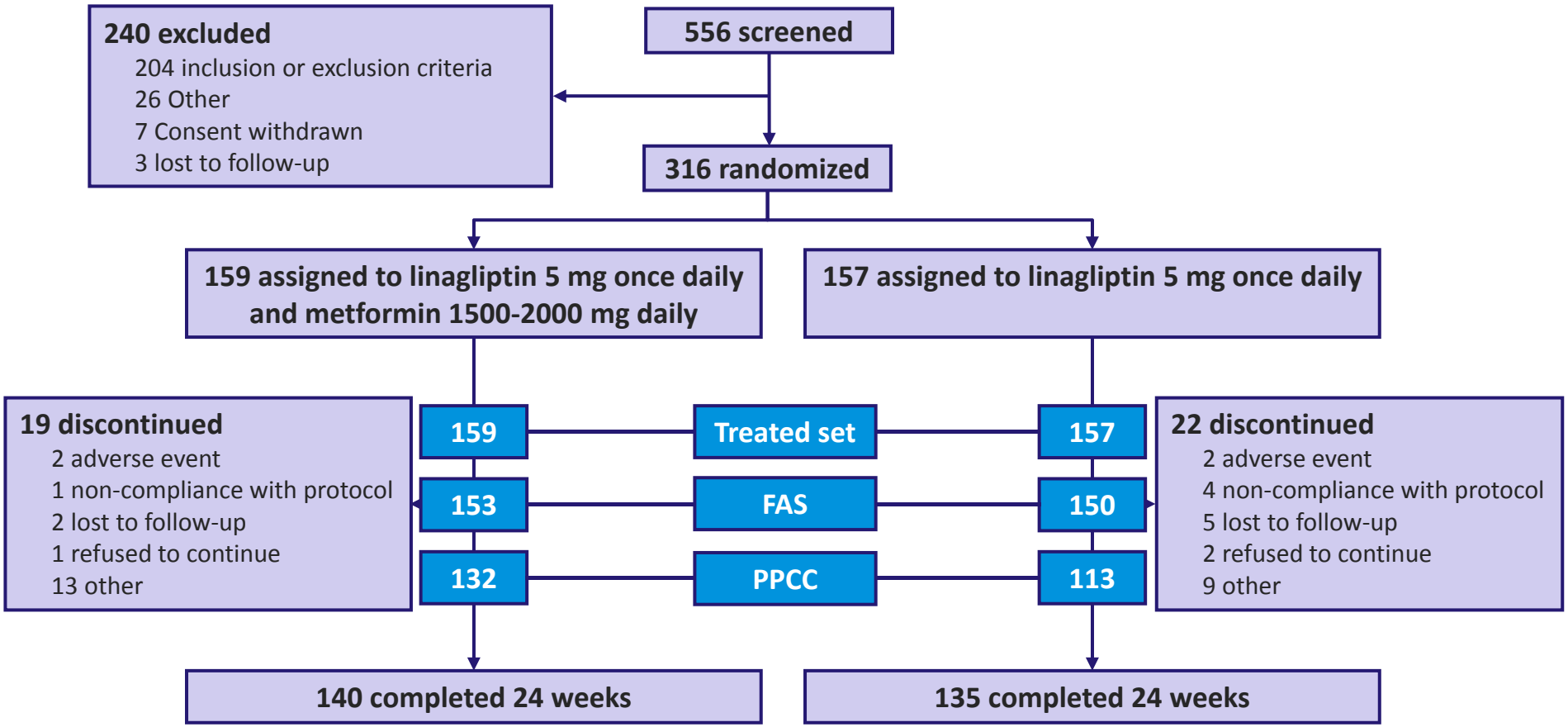
Back-up

Study design



Registered with ClinicalTrials.gov, NCT01512979

Patient disposition



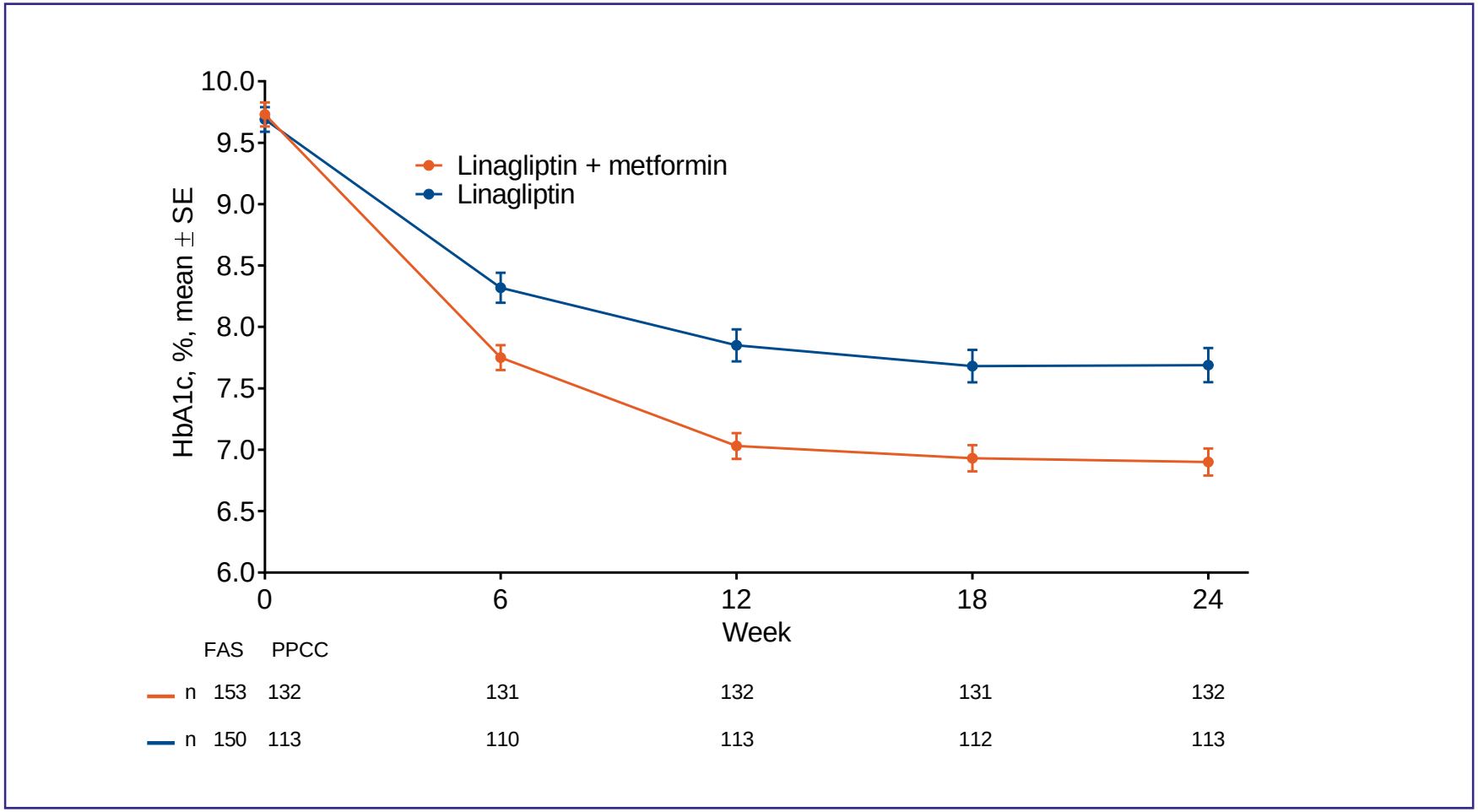
Treated set	**all randomized patients who received ≥1 dose of study drug**
FAS	**all randomized patients who received ≥1 dose of study drug, had a baseline HbA1c measurement and 1 on-treatment HbA1c measurement**
PPCC	**all randomized patients who received ≥1 dose of study drug, had a baseline HbA1c measurement, had no important protocol violations, completed 24 weeks of treatment without receiving glycemic rescue, and had an HbA1c measurement at Week 24**

Additional baseline characteristics

	Linagliptin + metformin	Linagliptin
Macrovascular disease, n (%)	67 (42.1)	72 (45.9)
Hypertension	65 (40.9)	69 (43.9)
Coronary artery disease	10 (6.3)	13 (8.3)
Peripheral artery disease	7 (4.4)	1 (0.6)
Cerebrovascular disease	7 (4.4)	9 (5.7)
Microvascular disease, n (%)	20 (12.6)	18 (11.5)
Neuropathy	14 (8.8)	13 (8.3)
Retinopathy	7 (4.4)	6 (3.8)
Nephropathy	2 (1.3)	2 (1.3)
Concomitant medication, n (%)	99 (62.3)	108 (68.8)
Antihypertensives	65 (40.9)	65 (41.4)
Lipid-lowering	30 (18.9)	33 (21.0)
Aspirin	22 (13.8)	20 (12.7)

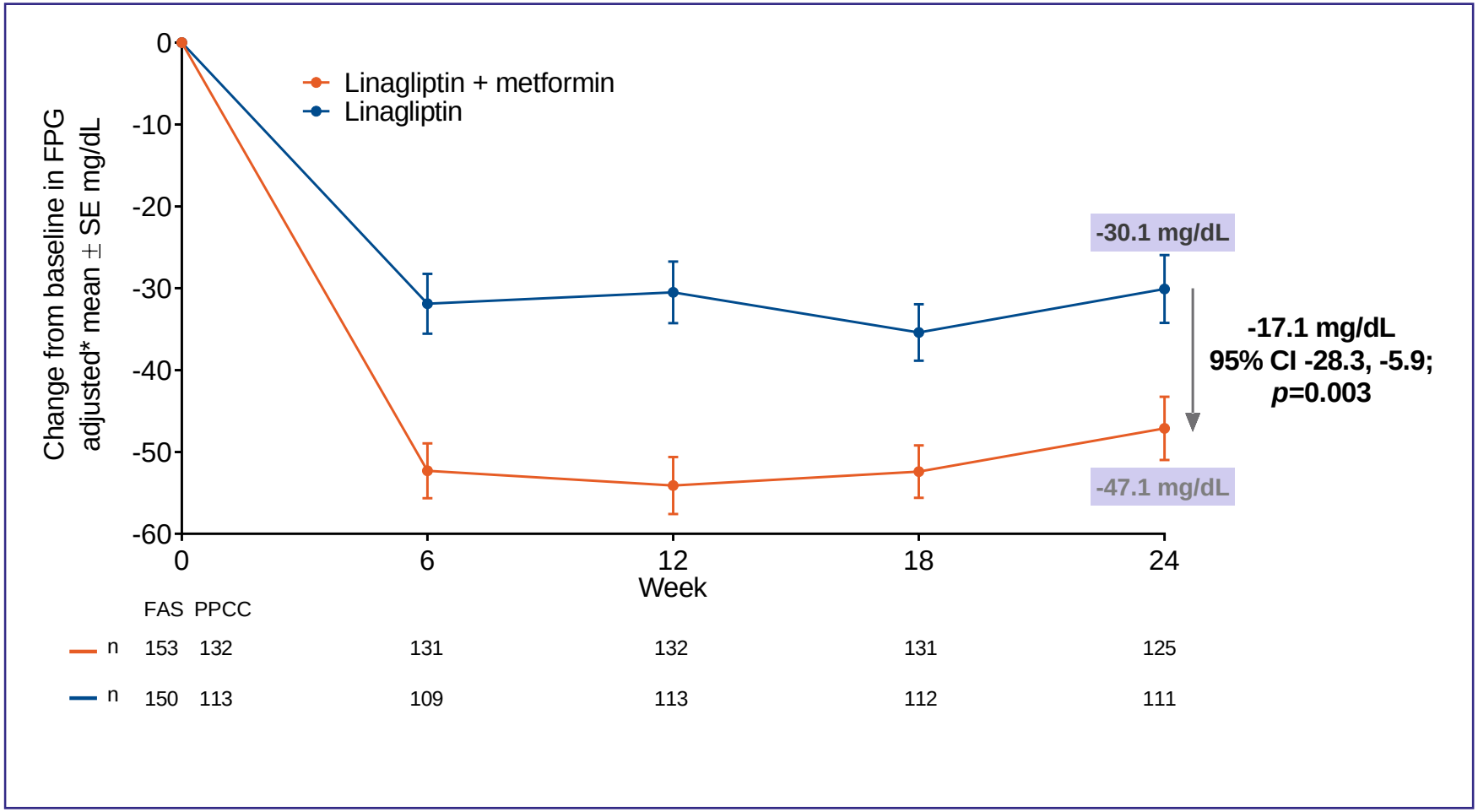
Data are for the treated set of patients (linagliptin and metformin: n=159; linagliptin: n=157)

HbA1c over time (PPCC): observed cases



PPCC = per-protocol completers cohort: all randomized patients who received ≥1 dose of study drug, had a baseline HbA1c measurement, had no important protocol violations, completed 24 weeks of treatment without receiving glycemic rescue, and had an HbA1c measurement at Week 24

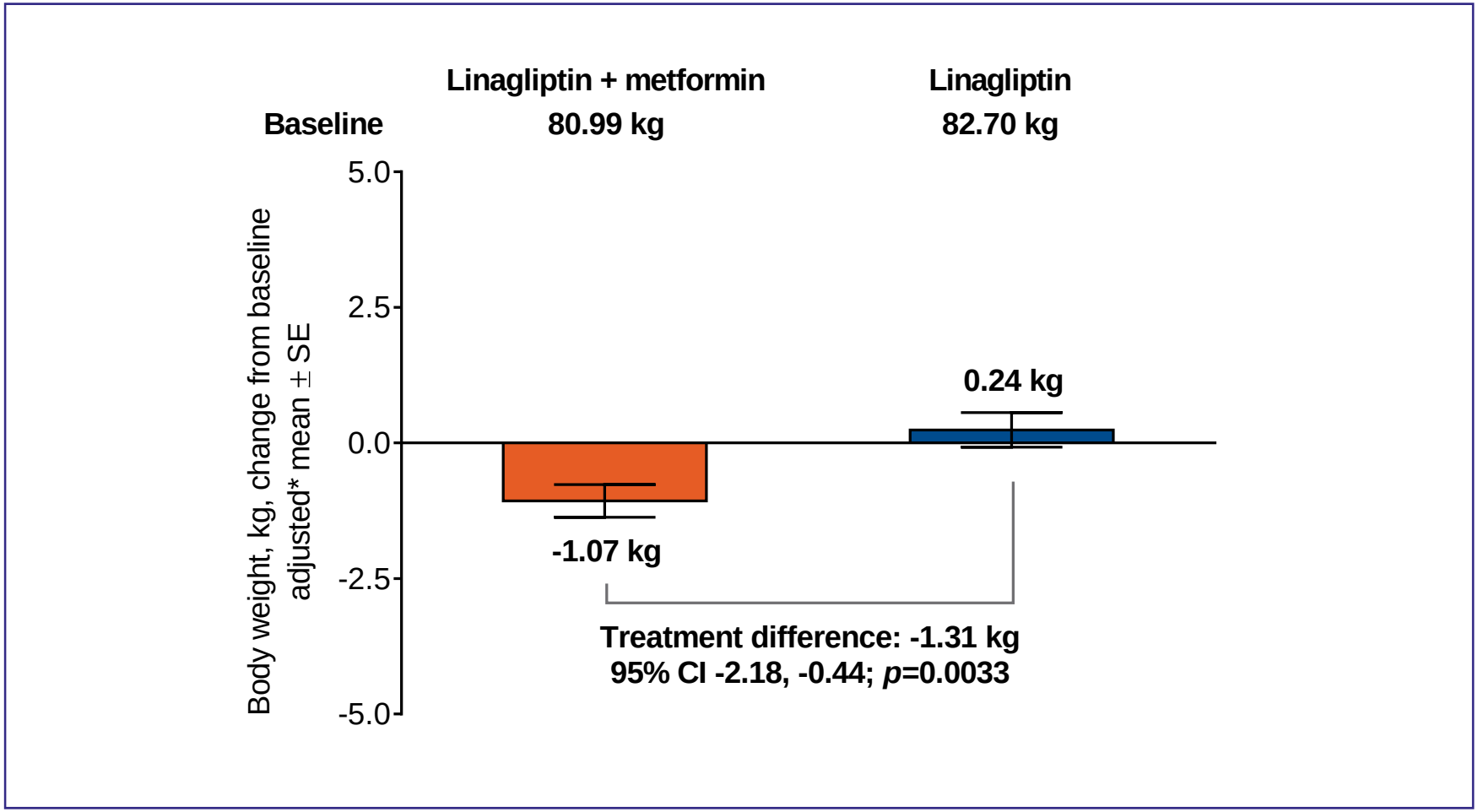
Change in fasting plasma glucose over time (PPCC): observed cases



*Mixed model for repeated measurements includes treatment, continuous baseline HbA1c, continuous baseline FPG, week repeated within patient, week-by-baseline-FPG interaction and week-by-treatment interaction

FPG = fasting plasma glucose; PPCC = per-protocol completers cohort: all randomized patients who received ≥1 dose of study drug, had a baseline HbA1c measurement, had no important protocol violations, completed 24 weeks of treatment without receiving glycemic rescue, and had an HbA1c measurement at Week 24

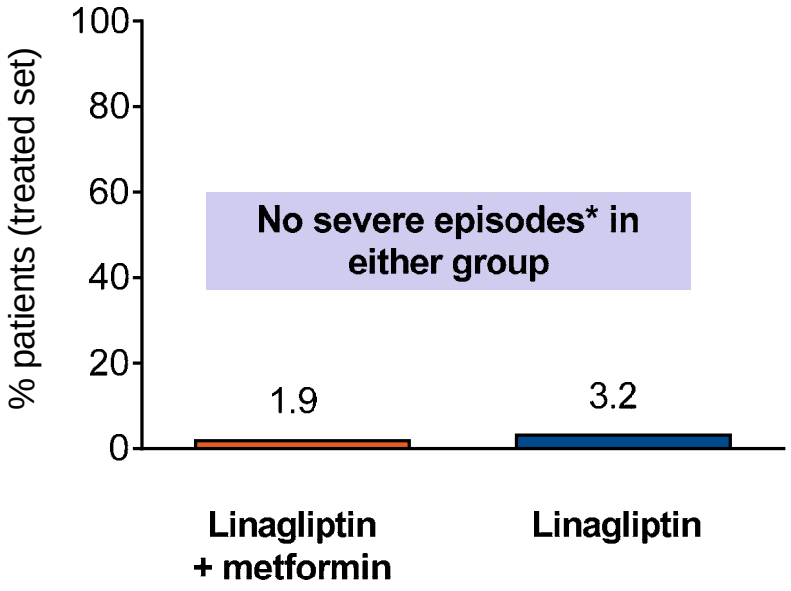
Change in body weight at Week 24



Analysis of covariance model with treatment, continuous baseline HbA1c and continuous baseline weight. PPCC = per-protocol completers cohort: all randomized patients who received ≥1 dose of study drug, had a baseline HbA1c measurement, had no important protocol violations, completed 24 weeks of treatment without receiving glycemic rescue, and had an HbA1c measurement at Week 24

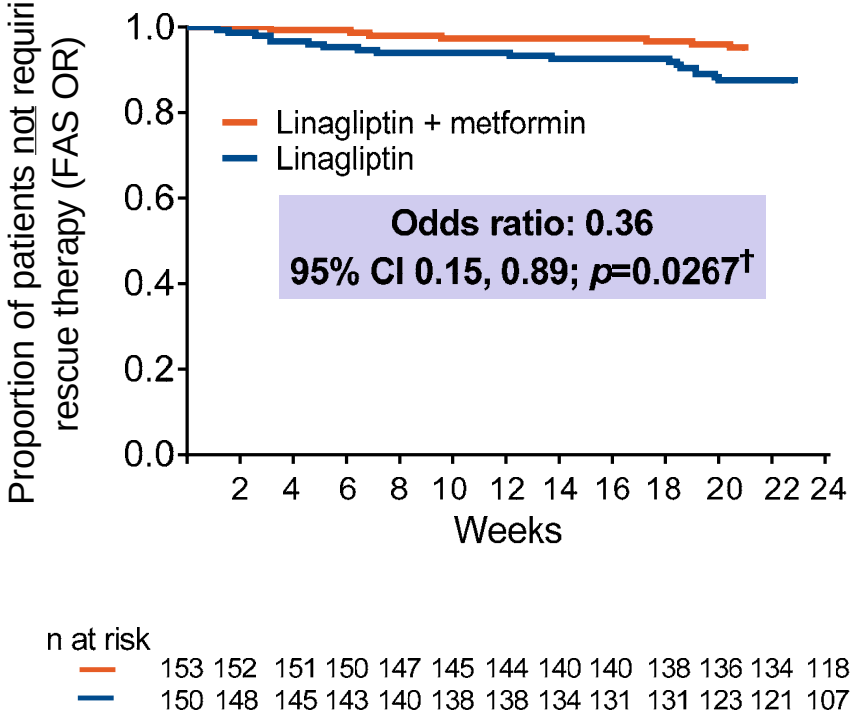
Hypoglycemia and glycemic rescue: 24 weeks

Investigator-reported hypoglycemia



*Episode requiring the assistance of another person to administer carbohydrate, glucagon, or other resuscitative action

Glycemic rescue treatment



Treated set: all randomized patients who received ≥1 dose of study medication

†Logistic regression model includes continuous baseline HbA1c and treatment

FAS = full-analysis set: all randomized patients who received ≥1 dose of study drug and had a baseline HbA1c measurement and ≥1 on-treatment HbA1c measurement; OR = original results