



OFFICIAL HIGHLIGHTS FROM THE AMERICAN DIABETES ASSOCIATION'S 79th SCIENTIFIC SESSIONS

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HIGHLIGHTS FROM THE 79TH ADA SCIENTIFIC SESSIONS

Myriam Z. Allende Vigo, MD CDE FACP FACE
Endocrinologist

Disclosure

- Has multiplicity of interests; no conflicts.
 - Has received honorarium as Speaker &/or Consultant for the following Pharmaceutical Companies: Abbvie & Merck.



OBJECTIVES

- Discuss findings & implications of clinical Trials

- CARMELINA



- CAROLINA



- PIONEER



The CARMELINA (**C**ardiovascular and **R**enal **M**icrovascular Outcom**E** Study With **LINA**gliptin) Trial



Objectives and study design

- The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) was designed to evaluate the CV safety and kidney outcomes of linagliptin in patients with type 2 diabetes at high cardiorenal risk.
- Randomized, double-blind, placebo-controlled, multicenter noninferiority trial conducted at 605 clinic sites in 27 countries, enrolling adults with type 2 diabetes and HbA_{1c} 6.5-10.0%.

Objectives and study design

- Participants also had high CV risk (history of vascular disease and urine-albumin creatinine ratio [UACR] >200mg/g) and high renal risk (reduced eGFR and micro- or macroalbuminuria; end-stage kidney disease [ESKD] was excluded).
- Patients were randomized to receive linagliptin (5 mg once daily; n = 3,494) or placebo (n = 3,485) added to usual care.
- Primary outcome was time to first occurrence of the composite of CV death, nonfatal myocardial infarction, or nonfatal stroke (3P-MACE).

Criteria for noninferiority of linagliptin vs. placebo was defined by the upper limit of the 2-sided 95% CI for the HR of linagliptin relative to placebo being less than 1.3.

Main findings

- Median follow-up was 2.2 years.
- The primary outcome occurred in 12.4% and 12.1% of patients in the linagliptin and placebo groups, respectively

Main findings

- There was no significant difference in the risk for all-cause mortality or non-CV death with linagliptin vs. placebo.
- Rates of hospitalization for heart failure did not differ between treatment groups: 6.0% and 6.5% in the linagliptin and placebo groups, respectively (P=0.26).
- The secondary renal outcome occurred in 9.4% and 8.8% of patients in the linagliptin and placebo groups, respectively (P = 0.62).

Main findings

- Linagliptin did not affect the risk for sustained $\geq 40\%$ reduction in eGFR, sustained ESKD, or death due to kidney disease, but significantly reduced the risk for progression to albuminuria (HR 0.86; 95% CI 0.78-0.95; P=0.0034).
- There were 9 (0.3%) vs. 5 (0.1%) events of adjudication-confirmed acute pancreatitis in the linagliptin and placebo groups, respectively.

Conclusions and clinical perspectives

- In patients with type 2 diabetes at high risk of CV events and a high prevalence of kidney disease, linagliptin added to usual care was noninferior to placebo added to usual care for the primary outcome of 3-point MACE and did not demonstrate evidence of CV benefit.
- There was no significant benefit of linagliptin compared with placebo for the incidence of the secondary kidney composite outcome.

Conclusions and clinical perspectives

- Linagliptin showed no increase in risk of hospitalization for heart failure, even in patients at high risk of heart failure.
- Linagliptin demonstrated a reassuring long-term kidney safety profile, with a reduction in progression of albuminuria.

CARdiovascular **O**utcomes Study of **LINA**gliptin vs glimepiride in patients with Type 2 Diabetes

Background

- Despite their use in the treatment of type 2 diabetes for decades, there is still controversy regarding the cardiovascular (CV) safety of sulfonylureas from both CV outcomes trials and observational studies.
- CAROLINA is the only active-comparator CV outcome trial for a DPP-4 inhibitor, comparing the long-term CV safety profile of linagliptin to glimepiride in patients with early type 2 diabetes and with increased CV risk.
- This trial adds evidence to the debate on the CV safety of sulfonylureas and also provides robust insights into the overall safety and efficacy of linagliptin and glimepiride in the long-term.

Objectives and study design

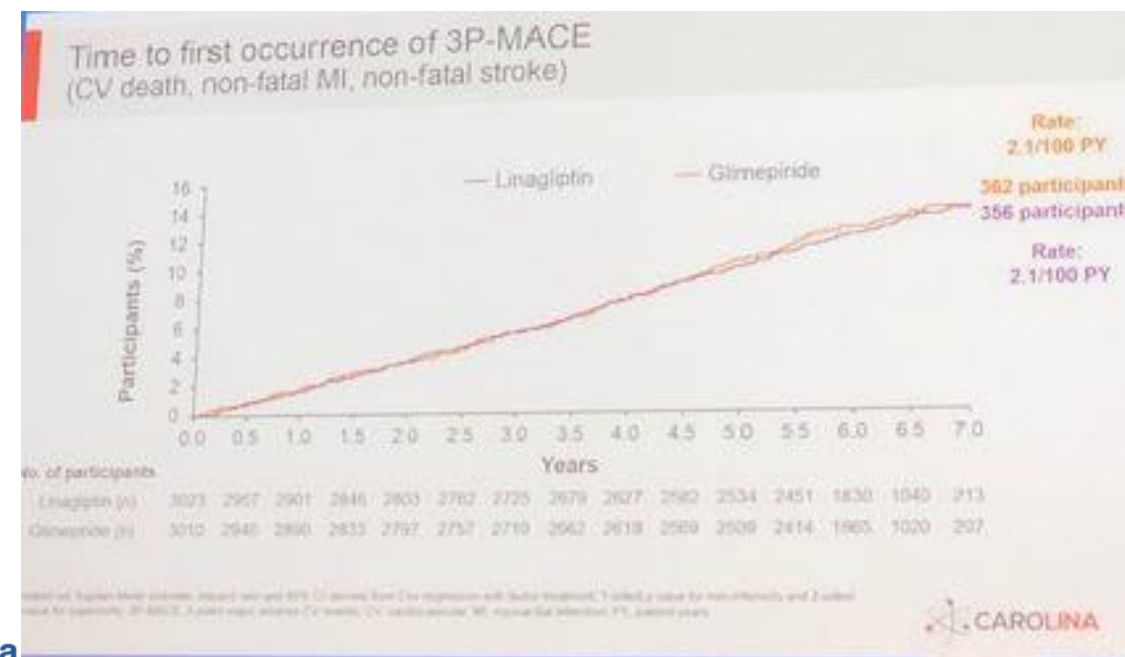
- **Glycemic inclusion criteria** were HbA_{1c} 6.5-8.5% if treatment-naïve or treated with metformin and/or an α -glucosidase inhibitor OR HbA_{1c} 6.5-7.5% if on sulfonylurea/glinide + metformin/ α -glucosidase inhibitor (≤ 5 years).
- **CV risk inclusion criteria** was one or more of the following: previous vascular disease, evidence of vascular-related end-organ damage, age ≥ 70 years, ≥ 2 CV risk factors.

Objectives and study design

- CAROLINA compared the long-term CV safety profile of linagliptin to glimepiride in patients with early type 2 diabetes at increased CV risk.
- Multinational, randomized, active-comparator CV outcomes trial.
- 6,033 patients were randomized to linagliptin (n=3,023) or glimepiride (n=3,010).

Objectives and study design

- Time to first occurrence of any of the following adjudicated components of the primary composite endpoint (3P-MACE, three-point major adverse CV event): CV death (including fatal stroke and fatal myocardial infarction [MI]), non-fatal MI (excluding silent MI), or non-fatal stroke.



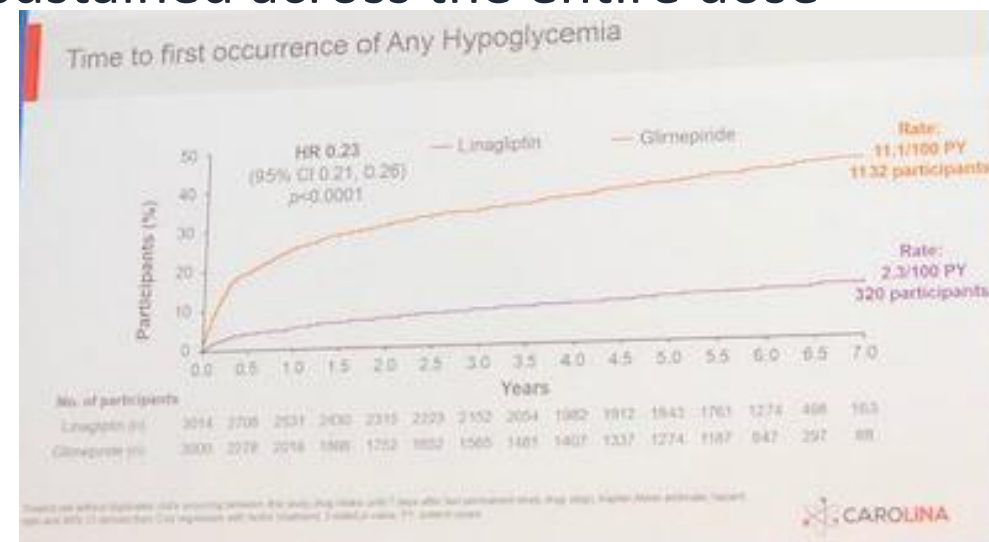
Main efficacy findings

- Median treatment exposure was 5.9 years for both groups.
- CAROLINA demonstrated non-inferiority for 3P-MACE of linagliptin vs. glimepiride in participants with relatively early type 2 diabetes and increased CV risk ($P < 0.0001$ for non-inferiority; $P = 0.76$ for superiority).
- Risk for CV mortality or overall mortality was not significantly different between groups:
 - HR 0.91 (95% CI 0.78-1.06) all-cause mortality.
 - HR 1.00 (95% CI 0.81-1.24) CV mortality.
 - HR 0.82 (95% CI 0.66-1.03) non-CV mortality.



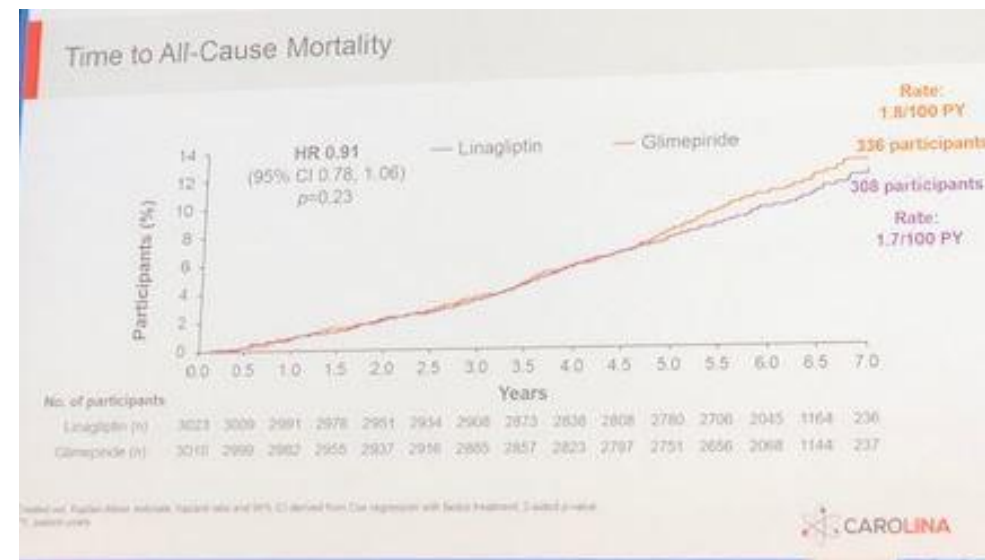
Main safety findings

- The frequency of adverse events, serious adverse events and adverse events leading to discontinuation of study drug were comparable between groups.
- The incidence of hypoglycemic events was substantially lower with linagliptin across all pre-defined hypoglycemia severity categories.
- Risk of hypoglycemia was increased early and sustained across the entire dose range for glimepiride.



Conclusions and clinical perspectives

- Cardiologists can be reassured about the CV safety profile of glimepiride.
- Linagliptin has a robustly demonstrated CV safety vs. glimepiride, with lower risk for hypoglycemia and weight gain.
- These results provide further evidence for the good safety and tolerability profile of linagliptin.





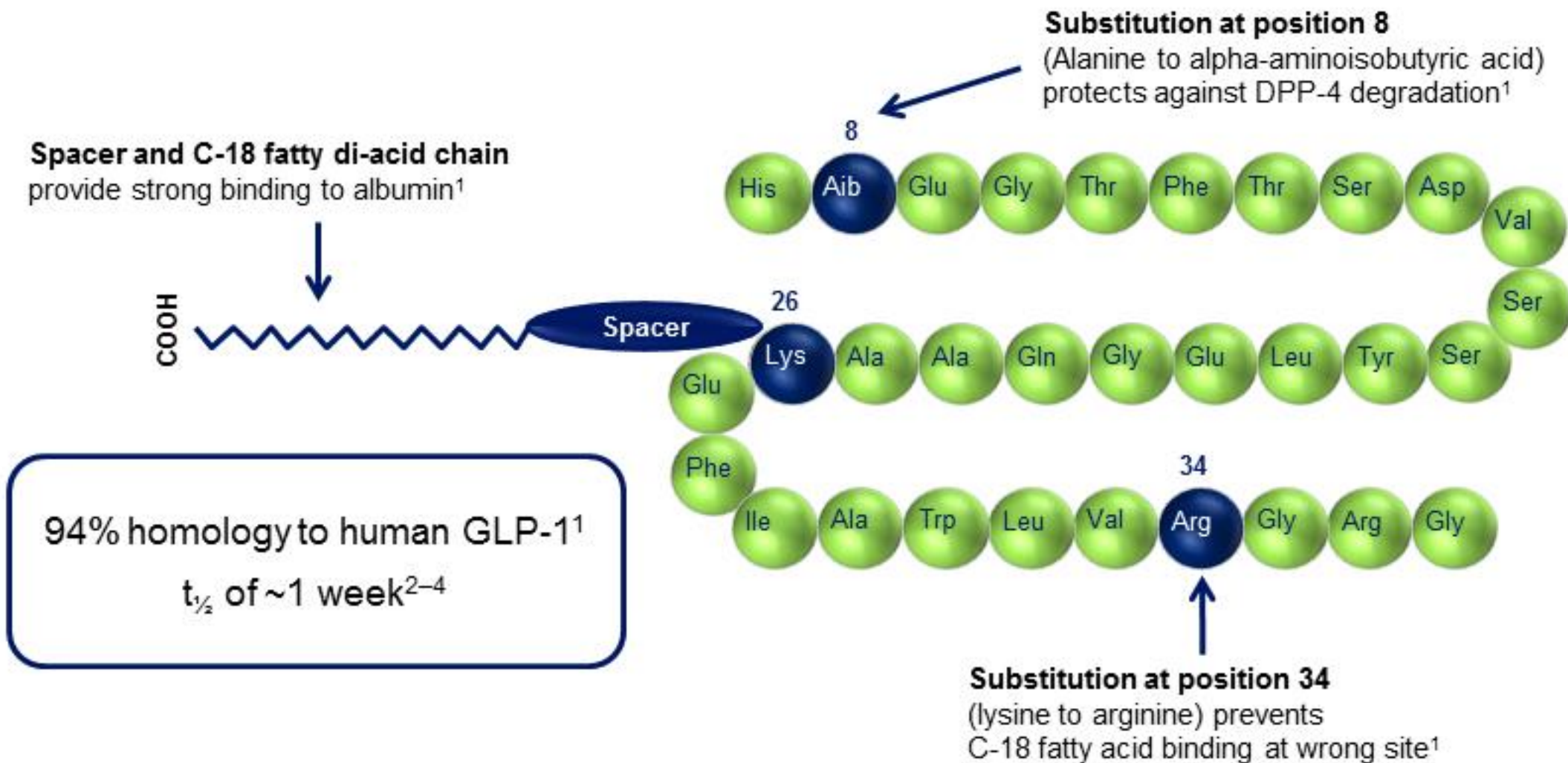
79TH
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Oral Semaglutide—The PIONEER Program Trials

Peptide InnOvation for Early Diabetes tReatment

Semaglutide: A human GLP-1 analog



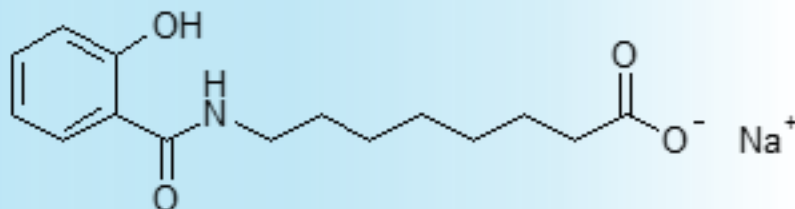
$t_{1/2}$, half-life.

1. Lau J et al. *J Med Chem* 2015;58:7370–80. 2. Kapitza C et al. *J Clin Pharmacol* 2015;55:497–504. 3. Marbury TC et al. *Diabetologia* 2014;57:S358.

Presented at the American Diabetes Association 79th Scientific Sessions, Session CT-SY12. June 11 2019, San Francisco, CA, USA

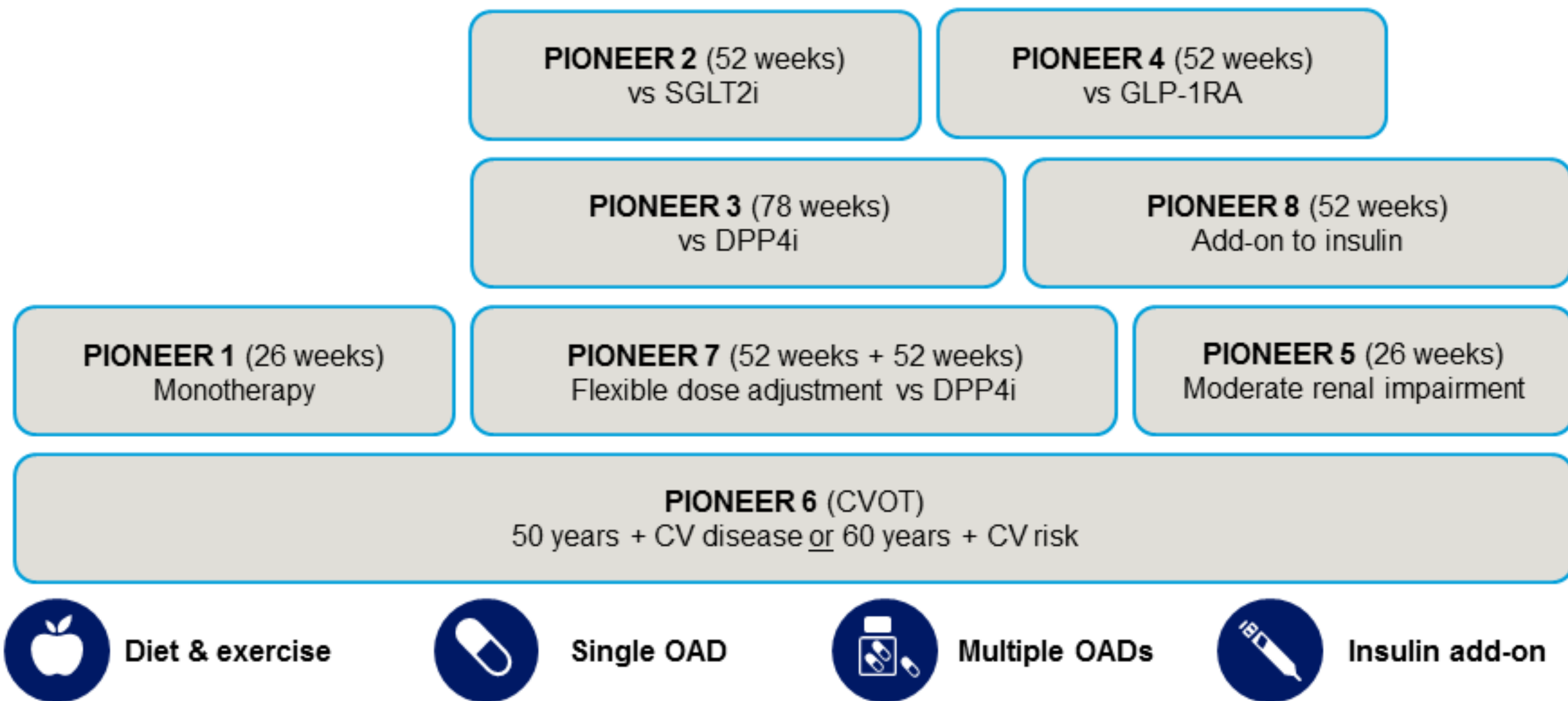
Oral semaglutide: Tablet co-formulation with SNAC

Sodium N-(8-(2-hydroxybenzoyl) Amino) Caprylate (SNAC)



- To achieve adequate bioavailability for oral administration, semaglutide is co-formulated with 300 mg of the absorption enhancer SNAC
- SNAC is a small fatty acid derivative that promotes absorption across the gastric epithelium
- SNAC causes a local increase of pH leading to higher semaglutide solubility and protection against proteolytic degradation

PIONEER clinical development program



CVOT, cardiovascular outcome trial; DPP4i, DPP-4 inhibitor; GLP-1RA, GLP-1 receptor agonist; Met, metformin; OAD, oral antidiabetic drug; SGLT2i, SGLT2 inhibitor; SoC, standard of care; SU, sulfonylurea.

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Introduction

- Semaglutide is the first tablet formulation of a glucagon-like peptide-1 receptor agonist (GLP1-RA). The PIONEER series of trials evaluated its efficacy and safety in several patient populations and vs. several other classes of therapies.
 - PIONEER 1: monotherapy vs. placebo.
 - PIONEER 2: vs. empagliflozin.
 - PIONEER 3: vs. sitagliptin.
 - PIONEER 4: vs. liraglutide.
 - PIONEER 5: moderate renal impairment.
 - PIONEER 6: cardiovascular outcomes trial.
 - PIONEER 7: flexible dose adjustment vs. sitagliptin.
 - PIONEER 8: add-on to insulin.

Baseline characteristics



Age



Sex, male



Duration of diabetes



BMI



HbA_{1c}



FPG

PIONEER 1
(monotherapy)

55 years

50.8%

3.5 years

31.8 kg/m²

8.0%

160 mg/dL

PIONEER 5
(moderate renal impairment)

70 years

48.1%

14.0 years

32.4 kg/m²

8.0%

164 mg/dL

PIONEER 8
(add-on to insulin)

61 years

54.0%

15.0 years

31.0 kg/m²

8.2%

153 mg/dL

Mean values reported. BMI, body mass index.

Aroda VR et al. *Diabetes Care*. 2019; [Accepted; In press]; Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;Epub ahead of print doi:10.1016/S2213-8587(19)30192-5;

Zinman B, et al. Poster 985-P. ADA 79th Annual Scientific Sessions. June 10, 2019.

Presented at the American Diabetes Association 79th Scientific Sessions, Session CT-SY12. June 11 2019, San Francisco, CA, USA

Baseline characteristics



Age



Sex, male



Duration of diabetes



BMI



HbA_{1c}



FPG

PIONEER 2	58 years	50.5%	7.4 years	32.8 kg/m ²	8.1%	173 mg/dL
PIONEER 3	58 years	52.8%	8.6 years	32.5 kg/m ²	8.3%	171 mg/dL
PIONEER 4	56 years	52.0%	7.6 years	33.0 kg/m ²	8.0%	167 mg/dL
PIONEER 7	57 years	56.5%	8.8 years	31.5 kg/m ²	8.3%	177 mg/dL

Mean values reported.

BMI, body mass index; FPG, fasting plasma glucose.

1. Montanya E, et al. Oral presentation 54-OR. ADA 79th Annual Scientific Sessions. June 08, 2019; 2. Rosenstock J et al. *JAMA* 2019;321:1–15; 3. Pratley R, et al. *Lancet* 2019;Epub ahead of print doi:10.1016/S0140-6736(19)31271-1; 4. Pieber TR et al. *Lancet Diabetes Endocrinol* 2019;Epub ahead of print doi:10.1016/S2213-8587(19)30194-9.

Presented at the American Diabetes Association 79th Scientific Sessions, Session CT-SY12. June 11 2019, San Francisco, CA, USA

Peptide InnOvation for Early Diabetes tReatment 1 trial (PIONEER 1)

PIONEER 1

Objectives and study design

- To compare the efficacy and safety of oral semaglutide as monotherapy with placebo in patients with type 2 diabetes.
- 26-week, randomized, double-blind, placebo-controlled, parallel-group trial.
- 703 patients randomized.

* the treatment effect in the target population regardless of trial product discontinuation or use of rescue medication

PIONEER 1

Objectives and study design

- To compare the efficacy and safety of oral semaglutide as monotherapy with placebo in patients with type 2 diabetes.
- 26-week, randomized, double-blind, placebo-controlled, parallel-group trial.
- 703 patients randomized.

* the treatment effect in the target population regardless of trial product discontinuation or use of rescue medication

PIONEER 1

Results

- Semaglutide significantly reduced HbA_{1c} (placebo-adjusted treatment differences at week 26: treatment policy estimand* **−0.6% [3 mg]**, **−0.9% [7 mg]**, **−1.1% [14 mg]**; $P < 0.001$ for all).
- Semaglutide reduced body weight (treatment policy estimand: **−0.1 kg [3 mg]**, **−0.9 kg [7 mg]**, **−2.3 kg [14 mg]**; $P < 0.001$).

* the treatment effect in the target population regardless of trial product discontinuation or use of rescue medication

PIONEER 1

Conclusion

- Oral semaglutide monotherapy demonstrated superior and clinically relevant improvements in HbA_{1c} (all doses) and body weight loss (14 mg dose) vs. placebo, with a safety profile consistent with other GLP-1 RAs.

* the treatment effect in the target population regardless of trial product discontinuation or use of rescue medication

Peptide InnOvation for Early Diabetes tReatment 2 trial (PIONEER 2)

PIONEER 2

Objectives and study design

- To compare the efficacy and safety of **oral semaglutide vs. empagliflozin** in patients with type 2 diabetes.
- 52-week, open-label trial.
- 816 patients randomized to oral semaglutide 14 mg or empagliflozin 25 mg.

PIONEER 2

Results

- **HbA_{1c} was reduced** by 1.4% at 26 weeks and 1.3% at 52 weeks compared to 0.9% and 0.8% with 25 mg empagliflozin at 26 and 52 weeks, respectively.
- The 14 mg dose of oral semaglutide demonstrated weight loss of 4.2 kg at 26 weeks and 4.7 kg at 52 weeks versus 3.8 kg with 25 mg empagliflozin at both 26 weeks and 52 weeks.
- The **increased weight loss** with oral semaglutide was statistically significant compared to empagliflozin at the 52-week time point.

PIONEER 2

Conclusion

- **Semaglutide is superior to empagliflozin in reducing HbA_{1c}, with less clear comparative effects on weight loss.**

PIONEER 3

Results

- Semaglutide, 7 and 14 mg/day, compared with sitagliptin, significantly reduced HbA_{1c} (P <0.001 for both) and body weight; (P <0.001 for both) from baseline to week 26.

PIONEER 3

Conclusion

- Oral semaglutide, 7 mg/day and 14 mg/day, compared with sitagliptin, resulted in significantly greater reductions in HbA_{1c} over 26 weeks, but there was no significant benefit with the 3-mg/day dosage.

Peptide InnOvation for Early Diabetes tReatment 4 trial (PIONEER 4)

PIONEER 4

Objectives and study design

- To compare the efficacy and long-term **adverse event profiles of oral semaglutide with subcutaneous liraglutide and placebo** in patients with type 2 diabetes.
- 26-week, randomized, double-blind, double-dummy trial.
- 711 adults with type 2 diabetes were randomized to receive oral semaglutide (n=285), subcutaneous liraglutide (n=284), or placebo (n=142).

PIONEER 4

Results

- Mean change from baseline in HbA_{1c} at week 26 was –1.2% (SE 0.1) with oral semaglutide, –1.1% (SE 0.1) with subcutaneous liraglutide, and –0.2% (SE 0.1) with placebo.
- Oral semaglutide was **non-inferior to subcutaneous liraglutide** in decreasing HbA_{1c} (P <0.0001) and superior to placebo (P <0.0001) by use of the treatment policy estimand.
- Semaglutide resulted in **superior weight loss** (–4.4 kg) compared with liraglutide (–3.1 kg; P=0.0003) and placebo (–0.5 kg P <0.0001) at week 26.
- Adverse events were more frequent with oral semaglutide (n=229 [80%]) and subcutaneous liraglutide (n=211 [74%]) than with placebo (n=95 [67%]).

PIONEER 4

Conclusion

- **Semaglutide was non-inferior** to subcutaneous liraglutide and superior to placebo in decreasing HbA_{1c}, and superior in decreasing body weight compared with both liraglutide and placebo at week 26.
- **Safety and tolerability of oral semaglutide were similar to subcutaneous liraglutide.**

Peptide InnOvation for Early Diabetes tReatment 5 trial (PIONEER 5)

PIONEER 5

Objectives and study design

- To investigate the efficacy and safety of oral semaglutide in patients with type 2 diabetes and **moderate renal impairment**.
- 26-week, randomized, double-blind, trial.
- 324 patients were assigned to oral semaglutide (n=163) or placebo (n=161).
- Renal inclusion criteria was an estimated glomerular filtration rate of **30-59 mL/min/1.73 m²**.

PIONEER 5

Results

- Semaglutide was superior to placebo in decreasing HbA_{1c} (estimated mean change of –1.0 percentage point (P <0.0001) and body weight; P <0.0001) by the treatment policy estimand.
- Safety, including renal safety, was consistent with the GLP-1 RA class.

PIONEER 5

Conclusion

- **Semaglutide was effective** in patients with type 2 diabetes and moderate renal impairment, potentially providing a new treatment option for this population.

Peptide InnOvation for Early Diabetes tReatment 6 trial (PIONEER 6)

PIONEER 6

Objectives and study design

- To investigate **CV outcomes** of once-daily semaglutide in an event-driven, randomized, double-blind, placebo-controlled trial.
- **CV inclusion criteria** were presence of high CV risk (age of ≥ 50 years with established CV or chronic kidney disease, or age of ≥ 60 years with CV risk factors only).
- 3,183 patients were randomly assigned to receive oral semaglutide or placebo.
- The primary outcome in a **time-to-event** analysis was the first occurrence of a major adverse CV event (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke).

PIONEER 6

Results

- Median time in the trial was 15.9 months.
- Major adverse CV events occurred in 61 of 1,591 patients (3.8%) in the oral semaglutide group and 76 of 1,592 (4.8%) in the placebo group ($P < 0.001$ for noninferiority).
- Results for components of the primary outcome were as follows: death from CV causes 15 of 1,591 patients (0.9%) in the semaglutide group and 30 of 1,592 (1.9%) in the placebo group (HR 0.49; 95% CI, 0.27 to 0.92); nonfatal myocardial infarction, 37 of 1,591 patients (2.3%) and 31 of 1,592 (1.9%), respectively (HR 1.18; 95% CI, 0.73 to 1.90); and nonfatal stroke, 12 of 1,591 patients (0.8%) and 16 of 1,592 (1.0%), respectively (HR 0.74; 95% CI, 0.35 to 1.57).

PIONEER 6

Conclusion

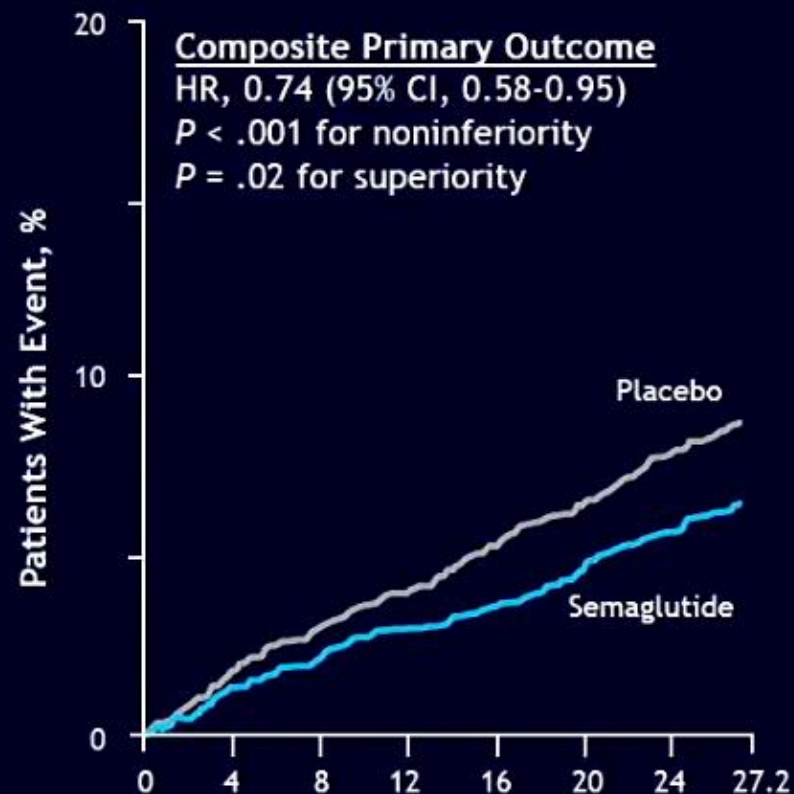
- The CV risk profile of oral semaglutide was not inferior to that of placebo.

Semaglutide CV outcomes

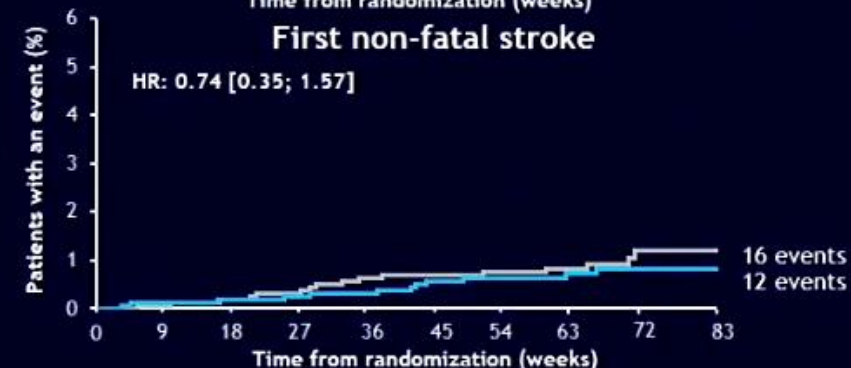
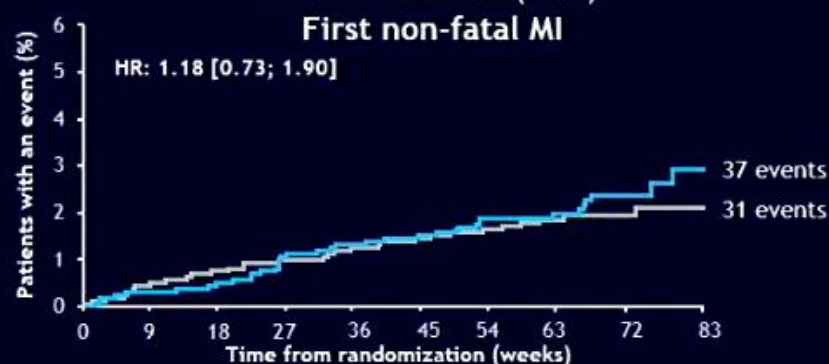
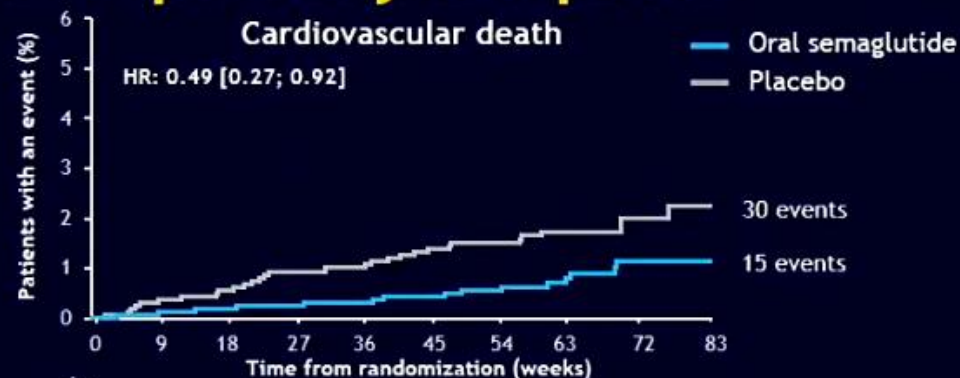
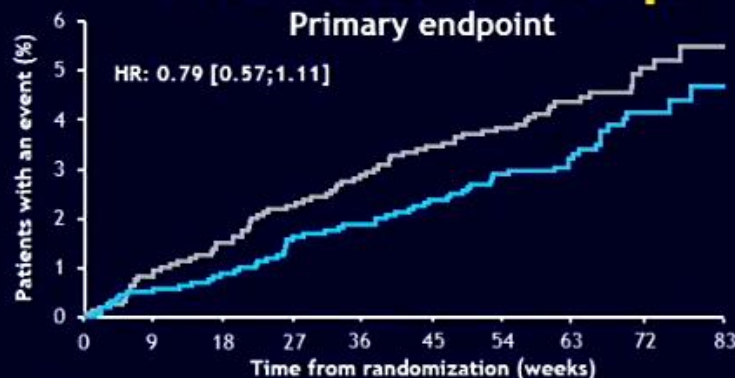
Trial design and characteristics

- N = 3297
- **Inclusion criteria:** ≥50 years old with established CVD, CHF, or CKD (stage 3 or higher) OR ≥60 years old with ≥1 CV risk factor
- Primary composite outcome: first occurrence of CV death, nonfatal MI, or nonfatal stroke
- Patient characteristics were similar across treatment groups (0.5 mg SEMA, 1.0 mg SEMA, and matched controls)
- Median observation time: 2.1 years

Effect on Risk of CV Event, HR (95% CI)				
All-Cause Mortality	CV Mortality	Nonfatal MI	Nonfatal Stroke	Hosp. for HF
1.05 (0.74-1.50)	0.98 (0.65-1.48)	0.74 (0.51-1.08)	0.61 (0.38-0.99) ^a	1.11 (0.77-1.61)



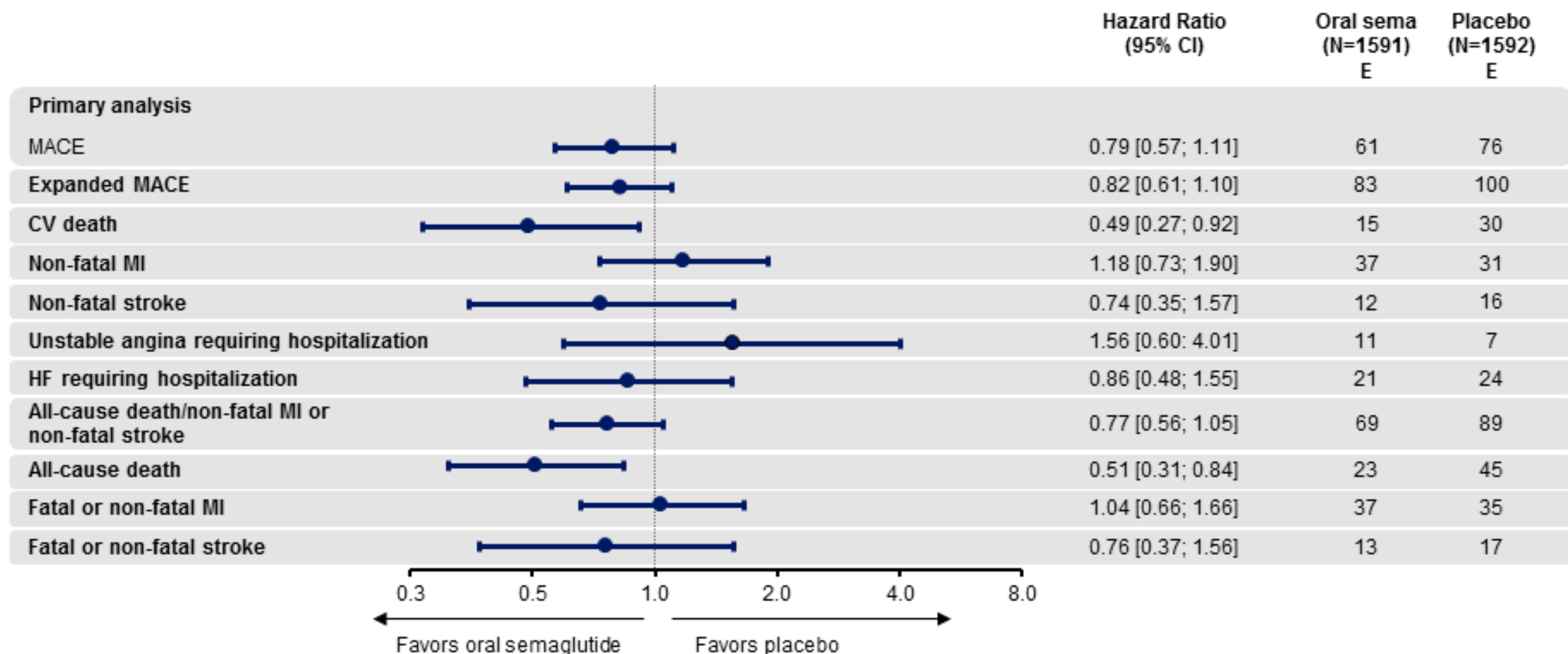
Individual components of primary endpoint



All events confirmed by EAC. Cumulative incidence estimate plot for EAC-confirmed events using 'in-trial' data from subjects in the full analysis set. Time from randomization to first event was analyzed using a Cox proportional hazards model with treatment as categorical fixed factor and stratified by evidence of CV disease at screening. Subjects were censored at the end of their in-trial observation period.

CV, cardiovascular; EAC, event adjudication committee; HR, hazard ratio; MI, myocardial infarction.

First event – secondary endpoints



All events confirmed by EAC. Hazard ratio with 95% confidence intervals, Cox proportional hazards model with treatment as factor, 'p-value': unadjusted two-sided p-value for test of no difference from 1.

CI, confidence interval; EAC, event adjudication committee; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

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Peptide InnOvation for Early Diabetes tReatment 7 trial (PIONEER 7)

PIONEER 7

Objectives and study design

- To compare the efficacy and safety of flexible dose adjustments of oral semaglutide with **sitagliptin 100 mg**.
- 52-week, multicenter, randomized, open-label, phase 3a trial.
- 504 patients were assigned to oral semaglutide (n=253) or sitagliptin (n=251).

*(i.e., the treatment effect in the target population had all patients remained on trial product and did not use rescue medication)

PIONEER 7

Results

- From a mean baseline HbA_{1c} of 8.3%, a greater proportion of participants achieved an **HbA_{1c} of less than 7%** with oral semaglutide than did with sitagliptin
- The odds of achieving an HbA_{1c} of less than 7% were significantly higher with semaglutide than sitagliptin (P <0.0001).
- The odds of **decreasing mean body weight** from baseline to week 52 were higher with semaglutide than with sitagliptin; (P <0.0001).
- The **safety profile was consistent** with subcutaneous GLP-1 RAs.

*(i.e., the treatment effect in the target population had all patients remained on trial product and did not use rescue medication)

PIONEER 7

Conclusion

- Oral semaglutide, with flexible dose adjustment, based on efficacy and tolerability, provided superior glycemic control and weight loss compared with sitagliptin

*(i.e., the treatment effect in the target population had all patients remained on trial product and did not use rescue medication)

Peptide InnOvation for Early Diabetes tReatment 8 trial (PIONEER 8)

PIONEER 8

Objectives and study design

- 52-week trial investigating the efficacy and safety of 3, 7, and 14 mg oral semaglutide compared with placebo in 731 people with type 2 diabetes treated with **insulin** and an average duration of diabetes of 15 years.
- During the first 26-week treatment period, the total daily insulin dose was not allowed to be increased above baseline followed by a 26-week period where the insulin treatment was adjusted without restrictions.

PIONEER 8

Results

- From a mean baseline of 8.2%, 3, 7, and 14 mg oral semaglutide achieved **reductions in HbA_{1c}** of 0.6%, 1.0% and 1.4% respectively, compared to no reduction (0.0%) in people treated with placebo, all in addition to insulin, at week 26, and 0.5%, 0.8%, and 1.2% respectively, compared with 0.0% at week 52.
- From a mean baseline body weight of 85.9 kg, people treated with 3, 7 and 14 mg semaglutide experienced a **weight loss** of 1.0 kg, 2.9 kg, and 4.3 kg, respectively, compared to a weight increase of 0.6 kg in people treated with placebo at week 52, all in addition to insulin.
- The total insulin dose at week 52 was increased by 2 units/day, reduced by 6 units/day and reduced by 7 units/day for people treated with 3, 7, and 14 mg semaglutide respectively, compared to an increase of 10 units/day for people treated with placebo.

PIONEER 8

Conclusion

- Oral semaglutide improved HbA_{1c} in patients with a long duration of diabetes and already treated with insulin, with the benefit of **clinically meaningful weight reduction, and without increasing the risk of hypoglycemia.**

Summary: Understanding oral semaglutide's effect



What is oral semaglutide's effect in adults with T2D?

Significant improvements in:

- HbA_{1c}
- Body weight (at higher doses)
- Fasting plasma glucose
- Achievement of clinical targets

What is oral semaglutide's safety and tolerability profile?

Similar safety profile as established GLP-1RAs, without any new safety signals

	HbA_{1c} reduction	Body weight reduction
3 mg	0.6–0.8%	1.3–1.7 kg
7 mg	1.0–1.2%	2.5–3.0 kg
14 mg	1.1–1.5%	3.7–4.1 kg
Placebo	0.0–0.1%	0.4–1.4 kg

Trial product estimands data at week 26 shown. AE, adverse event; GI, gastrointestinal; GLP-1RA, glucagon-like peptide-1 receptor agonist; SMBG, self-measured blood glucose. Aroda VR et al. *Diabetes Care*. 2019; [Accepted; In press]; Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;Epub ahead of print doi:10.1016/S2213-8587(19)30192-5; Zinman B, et al. Poster 985-P. ADA 79th Annual Scientific Sessions. June 10, 2019.

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PIONEER comparative studies: Conclusions



HbA_{1c}

Oral semaglutide superior vs:

- Empagliflozin
- Sitagliptin

Non-inferior vs:

- Liraglutide



Weight

Oral semaglutide superior vs:

- Sitagliptin
- Liraglutide

No difference vs:

- Empagliflozin

Safety

Overall incidence of AEs and SAEs similar for oral semaglutide compared to empagliflozin, sitagliptin and liraglutide

Hypoglycemia

Low rates of hypoglycemia and similar to empagliflozin, sitagliptin and liraglutide

GI tolerability

Rates of GI events consistent with the GLP-1RA class and higher than with empagliflozin and sitagliptin

First glance review of the results

- Confirms the efficacy of oral GLP-1 technology over the longer terms for glycemia, weight and CV risk factors
- Confirms better tolerability
- Suggests that oral semaglutide will become a major component of treatment of type 2 diabetes
- Has the potential to replace all injectable GLP-1 RAs
- Non-inferior on primary endpoint - lack of power for superiority or is it not as good as injectable?
- No reduction in MI or stroke - different from SUSTAIN 6 and LEADER (Why?)
 - are components of MACE good endpoints?
- RRR in mortality but absolute reduction is small - low number of events

and some limitations

- Provides pathophysiologic-based treatment
- Targets both fasting and postprandial glucose
- Single pill - may improve adherence
- Safe, effective initiation and no titration
- Less GI side effects of GLP-1
- Glycemia and CV benefits similar to Injectables
- **Need data on adherence in the real world**
- **Need a longer better powered study to determine equivalence to other GLP-1 RA on efficacy of CV event reduction**

Conclusions and clinical perspectives

- The PIONEER program confirms the efficacy of oral GLP-1 RA technology for reduction of HbA_{1c}.
- Oral semaglutide has the potential to replace all injectable GLP-1 RAs.

DPP4 inhibitor CVOTs: baseline characteristics

	SAVOR-TIMI 53 ¹		EXAMINE ²		TECOS ³		CAROLINA ^{®4}		CARMELINA ^{®5}
Mean age, years	65.1		61.0*		65.4		64.0		66.1
% with prior MI	38.0		87.5		42.7		13.8		58.1
% with prior HF	12.8		27.8		17.8		–		27
% with prior CVD	78.4		–		73.6		34.5		
Diabetes duration, y	10.3*		7.3*		11.6		6.2*		15
HbA _{1c} , %	8.0		8.0		7.2		7.2		7.9
Statin use, %	78.3		90.6		79.8		64.1		71.4
T2D therapy, %	Naive	4.1	Naive	1.1	Naive	–	Naive	9.2	Metformin 54.8 Sulfonylureas 34.9 Insulin 54.9
	Metformin	69.9	Metformin	65.0	Mono	47.7	Mono	66.0	
	SU	40.5	SU	46.9	Dual	51.4	Dual	23.8	
	TZD	6.2	TZD	2.5	TZD	–	TZD	–	
	Insulin	41.6	Insulin	29.4	Insulin	23.5	Insulin	Ex.	

Data are provided for the DPP4 inhibitor treatment arm. Mean values show unless otherwise indicated.

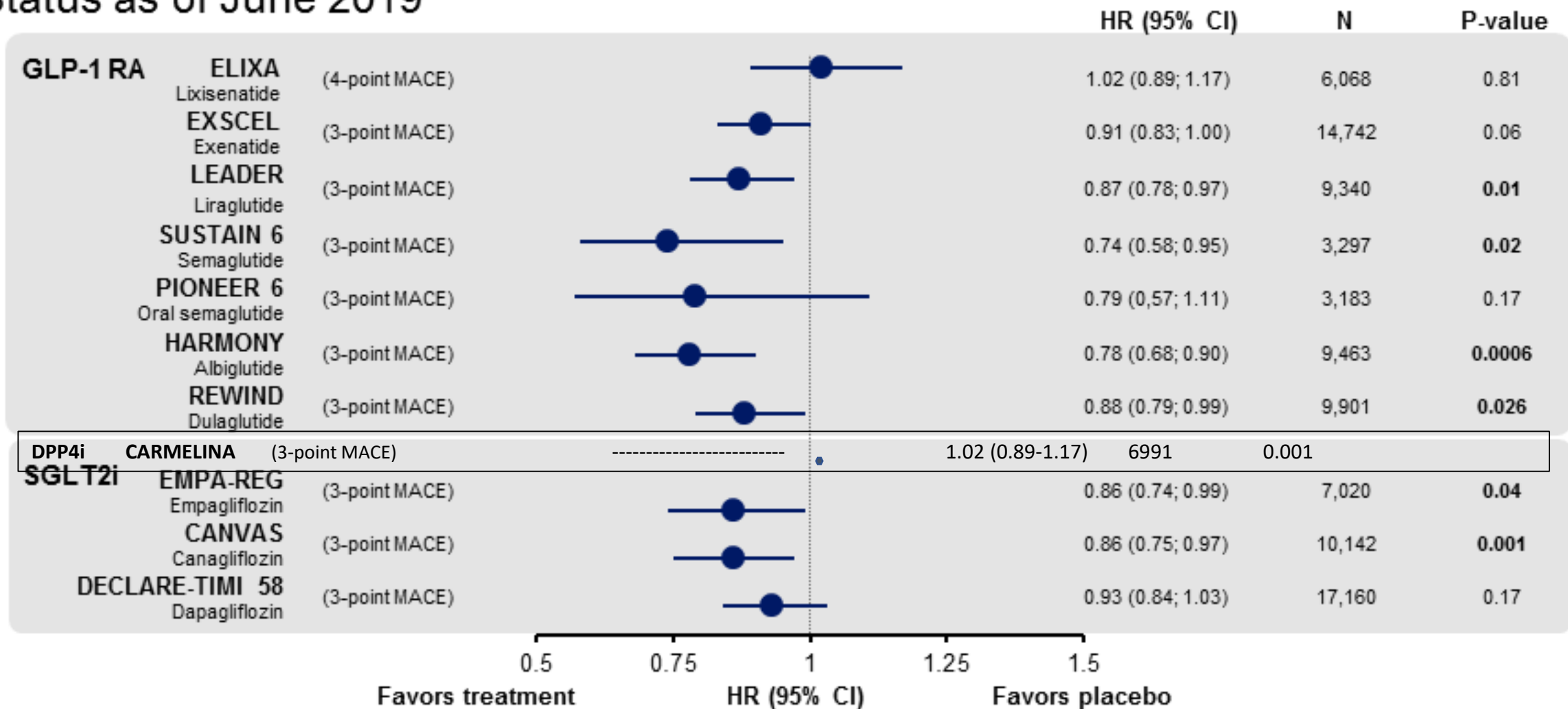
– indicates that the data are not reported.

*Median.

1. Scirica et al. N Engl J Med 2013;369:1337–46. 2. White et al. N Engl J Med 2013;369:1327–35. 3. Green et al. N Engl J Med 2015; DOI: 10.1056/NEJMoa1501302. 4. Mann et al. Diabetes Vasc Dis Res 2015;12:164–74. 5. NCJ2887532.

Overview of results from CVOT in T2D

Status as of June 2019



CI, confidence interval; CVOT, cardiovascular outcomes trial; GLP-1RA, GLP-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular event; SGLT2i, SGLT2 inhibitor. Adapted from Singh et al. *Indian J Endocrinol Metab* 2017;21:4–10; Holman et al. *N Engl J Med* 2017;377:1228–39; Neal et al. *N Engl J Med* 2017;377:644–57; Hernandez et al. *Lancet*; Epub ahead of print; Wiviott et al. *N Engl J Med* 2018; Epub ahead of print.

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Conclusions and clinical perspectives

- Trials show Non inferiority of **linagliptin, glimepiride and Oral semaglutide** on 3 point cardiovascular MACE.
- The PIONEER program confirms the efficacy of oral GLP-1 RA technology for reduction of HbA_{1c}.
- Oral semaglutide has the potential to replace all injectable GLP-1 RAs.
- **Oral semaglutide** would be the first non-injectable agent in the GLP-1 receptor agonist class; providing glycemic **control** along with **weight loss**.
- The study results would not necessarily be applicable to individuals without the features of the overall study population