**Dr. Kumar Abhisheka**
**Consultant Endocrinologist**
**AFCME New Delhi**

## Consultant Endocrinologist and Diabetologist in AFCME, New Delhi

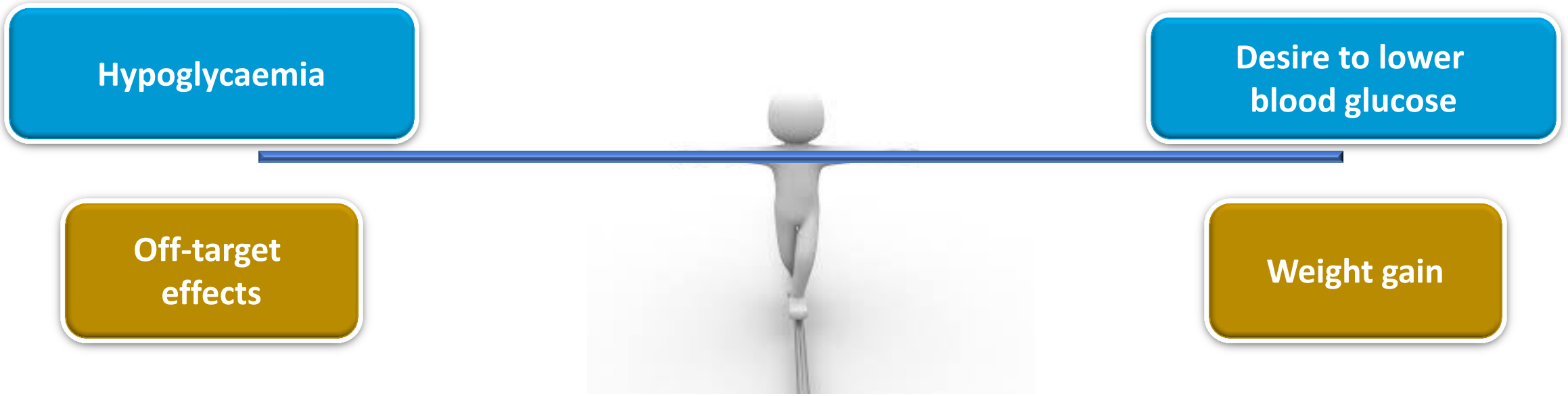
- Ex-Senior Resident Endocrinology at AIIMS, New Delhi
- Ex-Consultant Medicine, 7 AFH, Kanpur
- Wide clinical experience in treating endocrine disorders
- Publications in national medical journals
- Recipient of Young Investigator special merit award for oral presentation

# PIONEERing the paradigm shift in management of type 2 diabetes mellitus

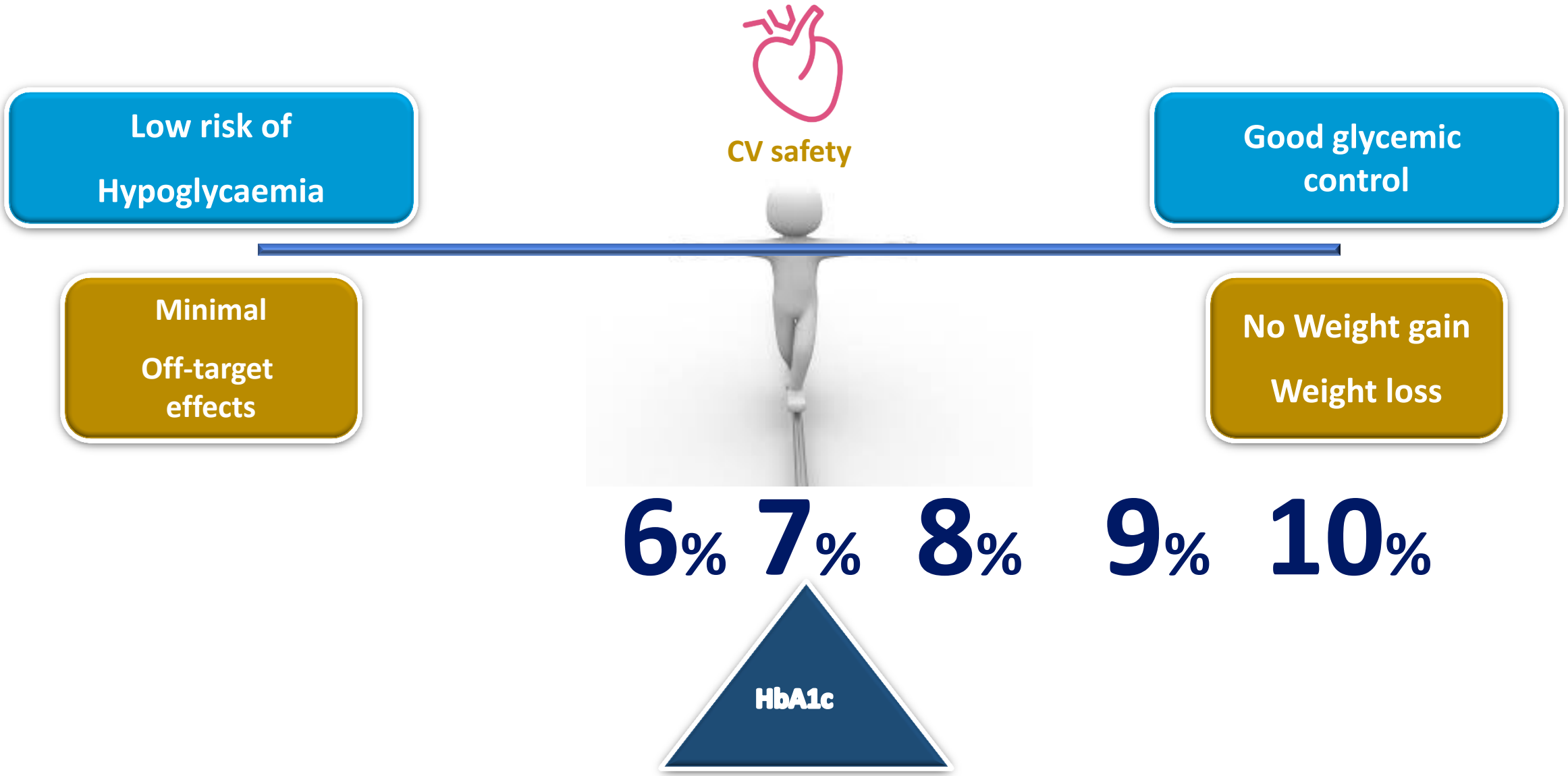
# Agenda

- Role of GLP-1 RAs in management of T2DM
- PIONEERing a new era: Triumphing targets with Oral Semaglutide
- PIONEERing management in routine clinical practice

# Quest for ideal anti-diabetic drug



# Our expectation from newer anti diabetic drugs



# The myriads of effects of GLP-1 in human body

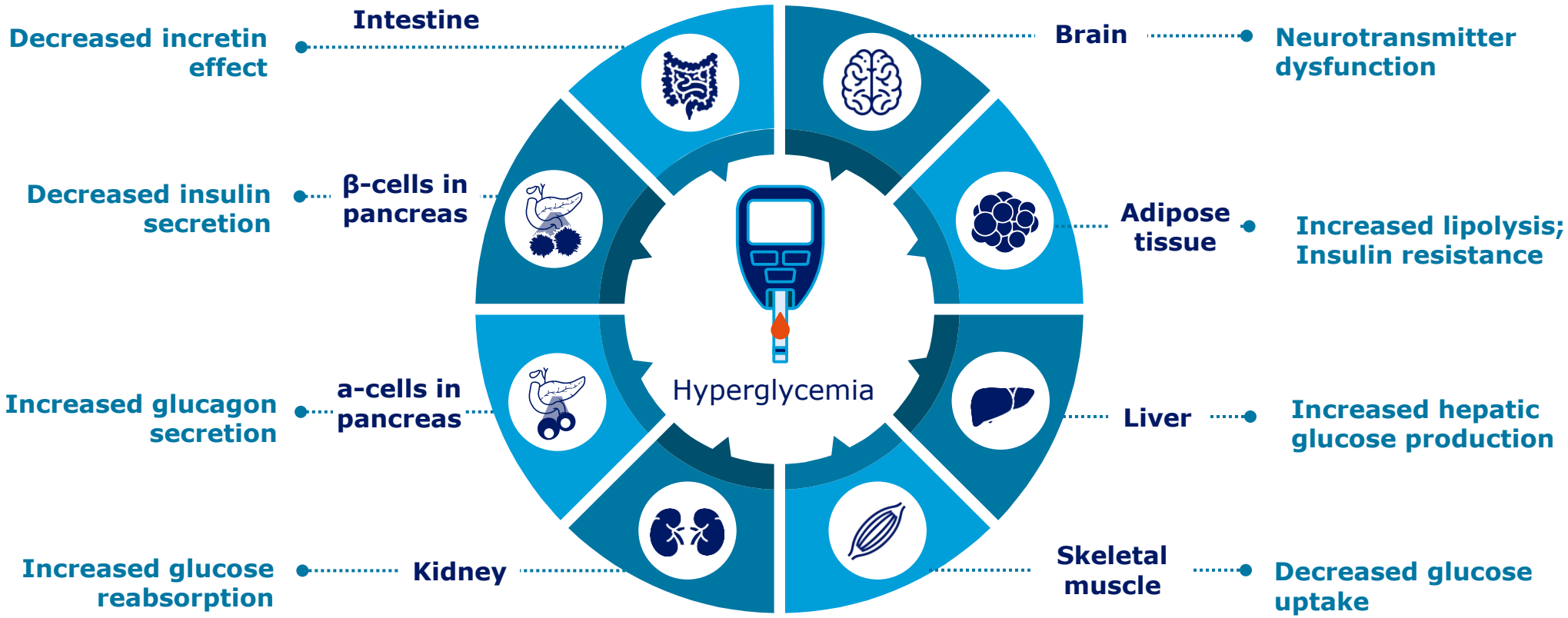
## ADDRESSING 6 OUT OF 8 OCTET MECHANISMS


GI, gastrointesntinal; GLP-1RA, glucagon-like peptide-1 receptor agonist.

1. Campbell JE, DJ Drucker. Cell Metab 2013;17:819–37; 2. Baggio LL, Drucker DJ. J Clin Invest 2014;124:4223–6; 3. Flint A et al. J Clin Invest 1998;101:515–20; 4. Blundell J et al. Diabetes Obes Metab 2017;19:1242–51; 5. Tong J, D'Alessio D. Diabetes 2014;63:407–9; 6. Armstrong MJ et al. J Hepatol 2016;64:399–408; 7. Armstrong MJ et al. Lancet 2016;387:679–90; 8. MacDonald PE et al. Diabetes 2002;51(Suppl 3):S434–42; 9. Drucker D. Cell Metab 2016;24:15–30.

# GLP-1 RAs target 6 of the 8 core defects evident in T2D

## ADDRESSING 6 OUT OF 8 OCTET MECHANISMS

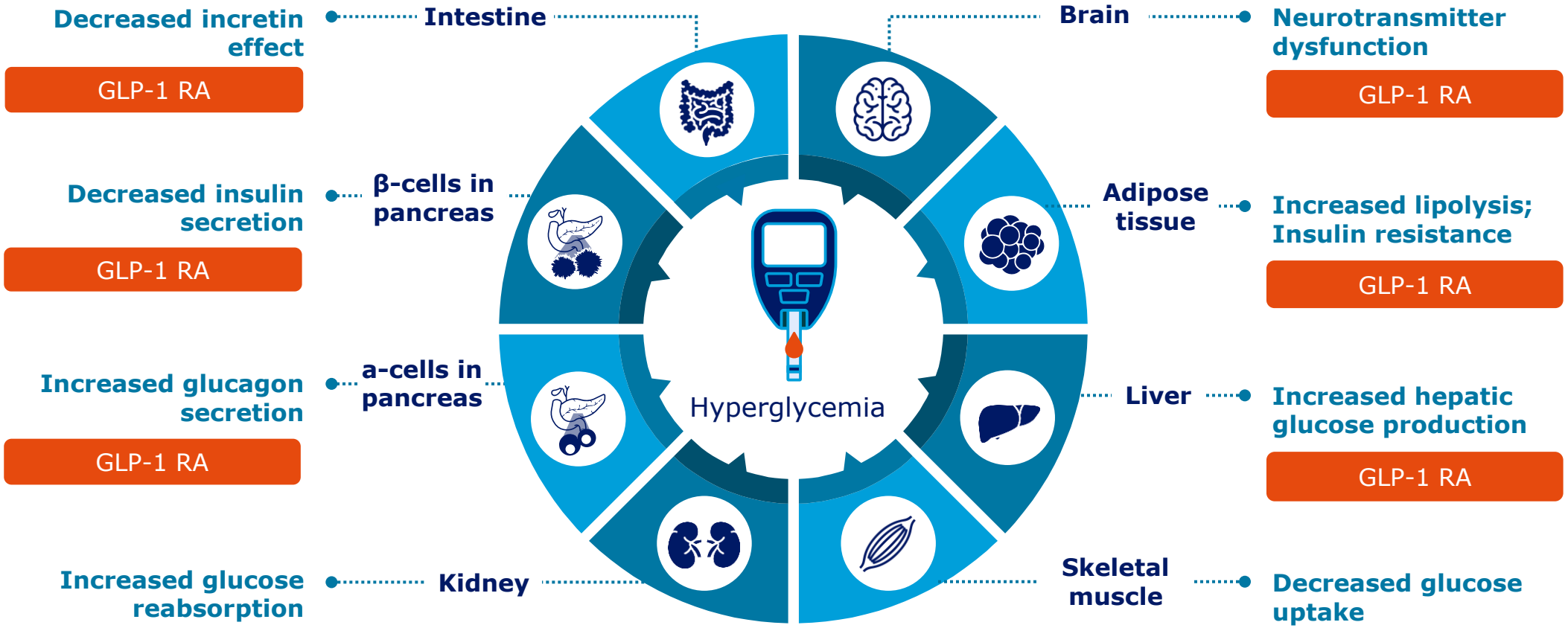



DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1 RA, glucagon like peptide-1 receptor agonist; SGLT2is, sodium glucose like cotransporter 2 inhibitors; SUs, sulfonylureas; TZDs, thiazolidinediones

1. Modified from DeFronzo RA et al. *Nat Rev Dis Primers.* 2015;1:15019; 2. Meier JJ. *Nat Rev Endocrinol*. 2012;8:728–742; 3. American Diabetes Association. *Diabetes Care*. 2020; 43 (Supplement 1):S1-S212; 4. Cornell S. J Clin Pharm Ther. 2020;45(Suppl 1):17–27

# GLP-1 RAs target 6 of the 8 core defects evident in T2D

## ADDRESSING 6 OUT OF 8 OCTET MECHANISMS




DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1 RA, glucagon like peptide-1 receptor agonist; SGLT2is, sodium glucose like cotransporter 2 inhibitors; SUs, sulfonylureas; TZDs, thiazolidinediones

1. Modified from DeFronzo RA et al. *Nat Rev Dis Primers.* 2015;1:15019; 2. Meier JJ. *Nat Rev Endocrinol*. 2012;8:728–742; 3. American Diabetes Association. *Diabetes Care*. 2020; 43 (Supplement 1):S1-S212; 4. Cornell S. J Clin Pharm Ther. 2020;45(Suppl 1):17–27

# In quest for an Ideal anti diabetic drug

## GLP-1 RAs: Holistic Approach

| | SU | TZD | AGI | DPP-4i | SGLT-2i | GLP-1 RA | Insulin |
|---|---|---|---|---|---|---|---|
| Physiological action(s) | ↑ Insulin secretion | ↑ Insulin sensitivity | Delays absorption of sugars from gut | ↑ Insulin secretion<br>↓ Glucagon secretion | ↓ Glucose reabsorption | ↑ Insulin secretion<br>↓ Glucagon secretion<br>Slows gastric emptying<br>↑ Satiety | ↑ Glucose disposal<br>↓ Hepatic glucose production |
| Efficacy (↓HbA1c) | High | High | Low | Intermediate | Intermediate | High | Highest |
| Hypoglycaemia risk | Moderate | Low | Low | Low | Low | Low | Low |
| Weight effect | ↑ | ↑ | ↔ | ↔ | ↓ | ↓ | ↑ |
| CV benefit | ↔ | ↔ | | ↔ | + | + | ↔ |

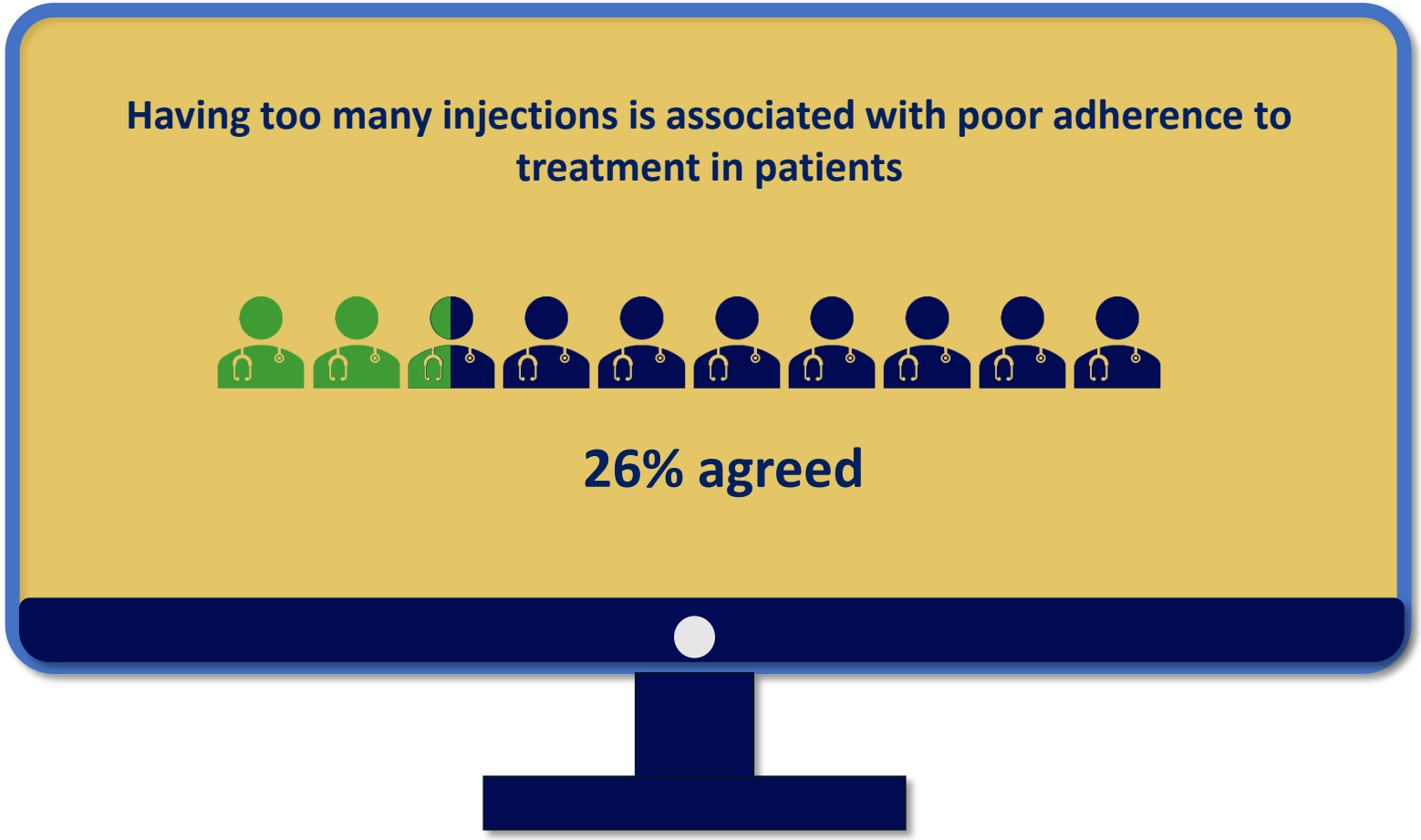
Adapted from Inzucchi SE et al. Diabetologia 2015;58:429–442; ADA Standards of Care. Diabetes Care; Dabhi AS et al. J Clin Diagn Res. 2013;7(12): 3023–3027

# The Challenge…

**LARGE MOLECULES – INJECTIONS**

Fear of injections may still remain a barrier to the use of a GLP-1RA[1] in **both** patients and physicians

A global internet survey of 1,250 physicians reported:[2]




*GLP-1RA, glucagon-like peptide-1 receptor agonist.*

*1. Østergaard L et al. Expert Rev Clin Pharmacol 2016;9:241–65; 2. Peyrot M et al. Diabet Med 2012;29:682–9.*

*Presented online at the European Association for the Study of Diabetes (EASD) - 56th Annual Meeting, 21-25 September 2020*

S/c Semaglutide is not available/marketed in India

# What do patients prefer?

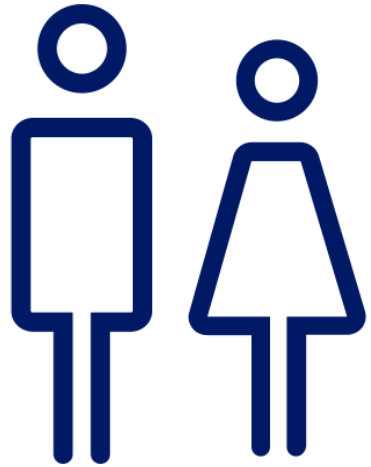
## UNDERSTANDING PATIENT PREFERENCE

Vial and syringe

Tailored engineered pen injectors

Oral tablet form

Increasing patient convenience



# Agenda

- Role of GLP-1 RAs in management of T2DM
- PIONEERing a new era: Triumphing targets with Oral Semaglutide
- PIONEERing management in routine clinical practice

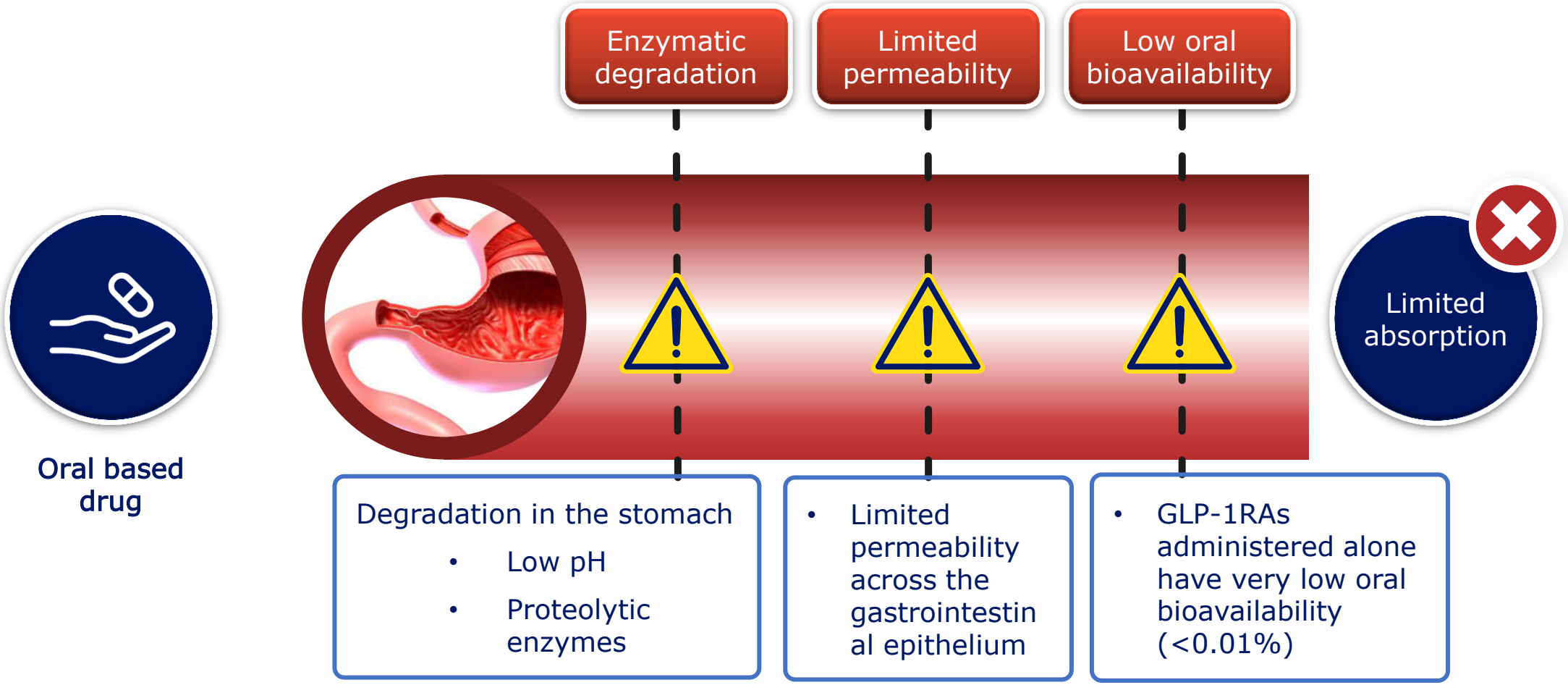
# The rationale for oral delivery of peptides

Unmet need for safe, non-invasive & convenient mode of therapy

- Improved patient compliance and expand treatment options
- Early commencement of treatment; better patient outcomes
- Address barriers associated with s.c. administration

# The quest  for first ever Oral GLP-1 RA

## The oral administration of peptides is challenging



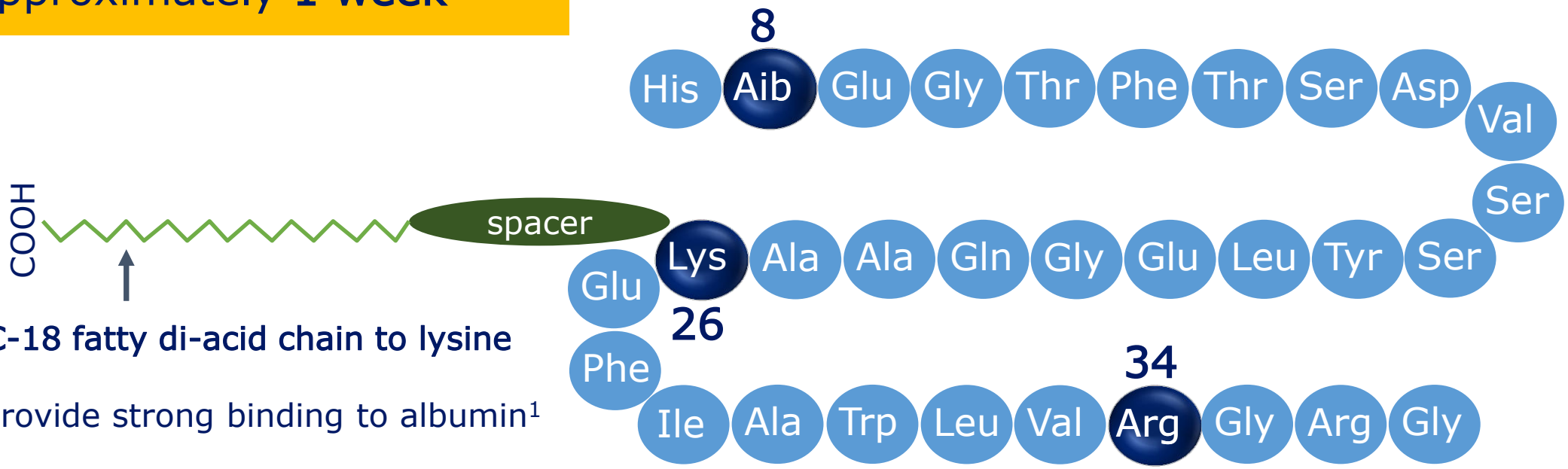

Renukuntla J et al. Int J Pharm 2013;447:75–93; Buckley ST et al. Sci Transl Med 2018;10(467): pii: eaar7047

# Semaglutide

## The foundation stone for "Peptide in a Pill"

- **94%** homology to human GLP-1[1]
- $t_{½}$ of approximately **1 week**[2,3]

**Amino acid substitution at position 8**
(alanine to alpha-aminoisobutyric acid)
protects against DPP-4 degradation[1]




**Spacer and C-18 fatty di-acid chain to lysine in position 26** provide strong binding to albumin[1]

**Amino acid substitution at position 34**
(lysine to arginine) prevents C-18 fatty di-acid binding at the wrong site[1]

**Semaglutide was the discovery which led to the path breaking innovation in bringing GLP-1 RAs in a pill**

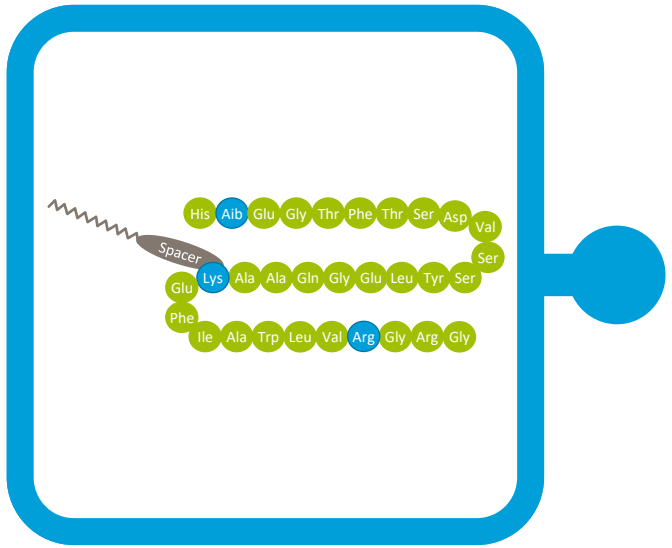
*DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; t½, half-life.*
*1. Lau J et al. J Med Chem 2015;58:7370–7380; 2. Kapitza C et al. J Clin Pharmacol 2015;55:497–504; 3. Marbury TC et al. Clin Pharmacokinet 2017;56:1381–1390.*

Semaglutide sc is not available/marketed in India

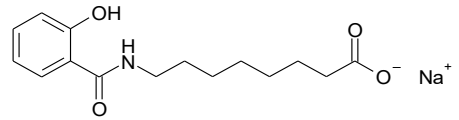
# Semaglutide in an oral formulation

## Co-formulation with absorption enhancer, SNAC

**Semaglutide:** a human GLP-1 analogue




**SNAC:** an absorption enhancer




- The most effective GLP-1RA tested to date[1–3]
- Long half-life (~1 week)[4]
- Promotes semaglutide absorption across the gastric epithelium[5]
- Enhances semaglutide oral bioavailability[5]

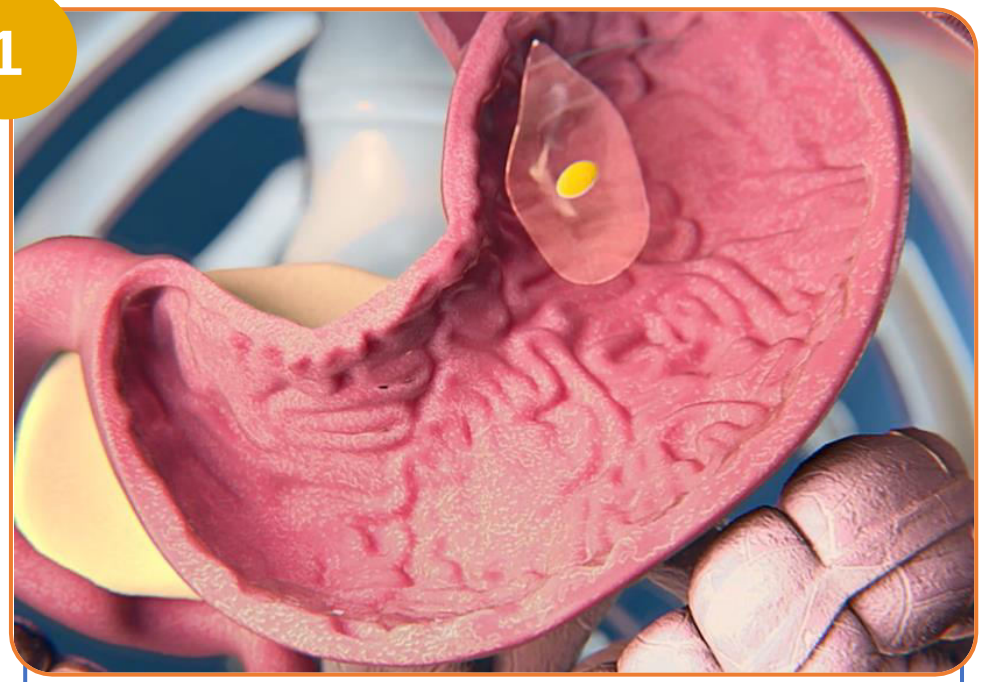
SNAC, sodium N-(8-(2-hydroxybenzoyl) amino) caprylate

1. Ahmann AJ et al. Diabetes Care 2018;41:258–266; 2. Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–286; 3. Capehorn MS et al. Diabetes Metab 2019;46:100–109; 4. Overgaard R et al. Diabetes Ther 2019;10:649–662; 5. Buckley ST et al. Sci Transl Med 2018;10(467): pii: eaar7047

# Mechanism of absorption of oral semaglutide

## pH buffer protection of semaglutide

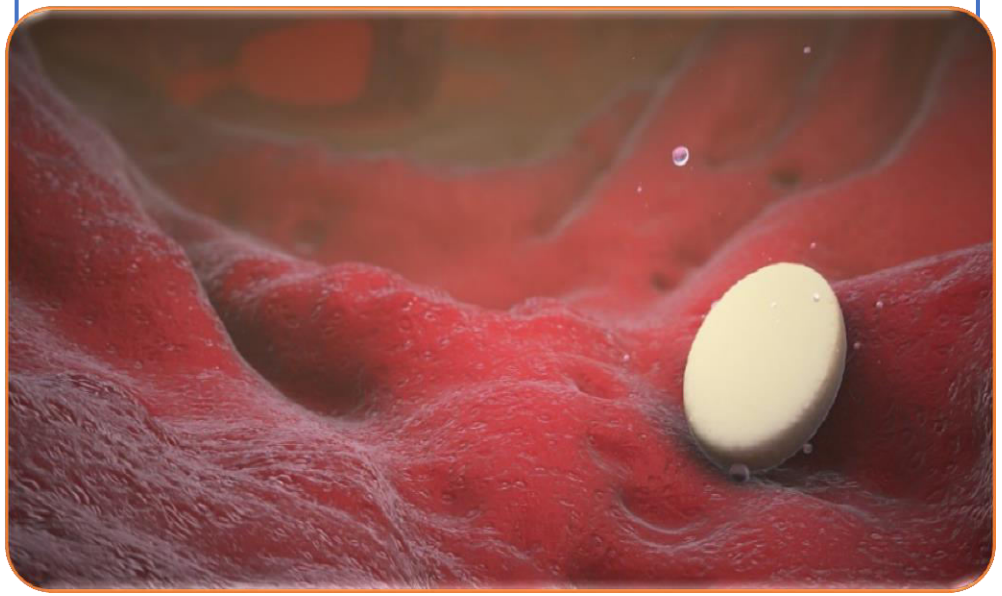
1



Absorption of oral semaglutide in stomach requires co-formulation with SNAC

2

SNAC causes a local increase of pH leading to higher solubility and protection from proteolytic degradation



SNAC: Sodium N-(8-(2-hydroxybenzoyl) amino) caprylate.

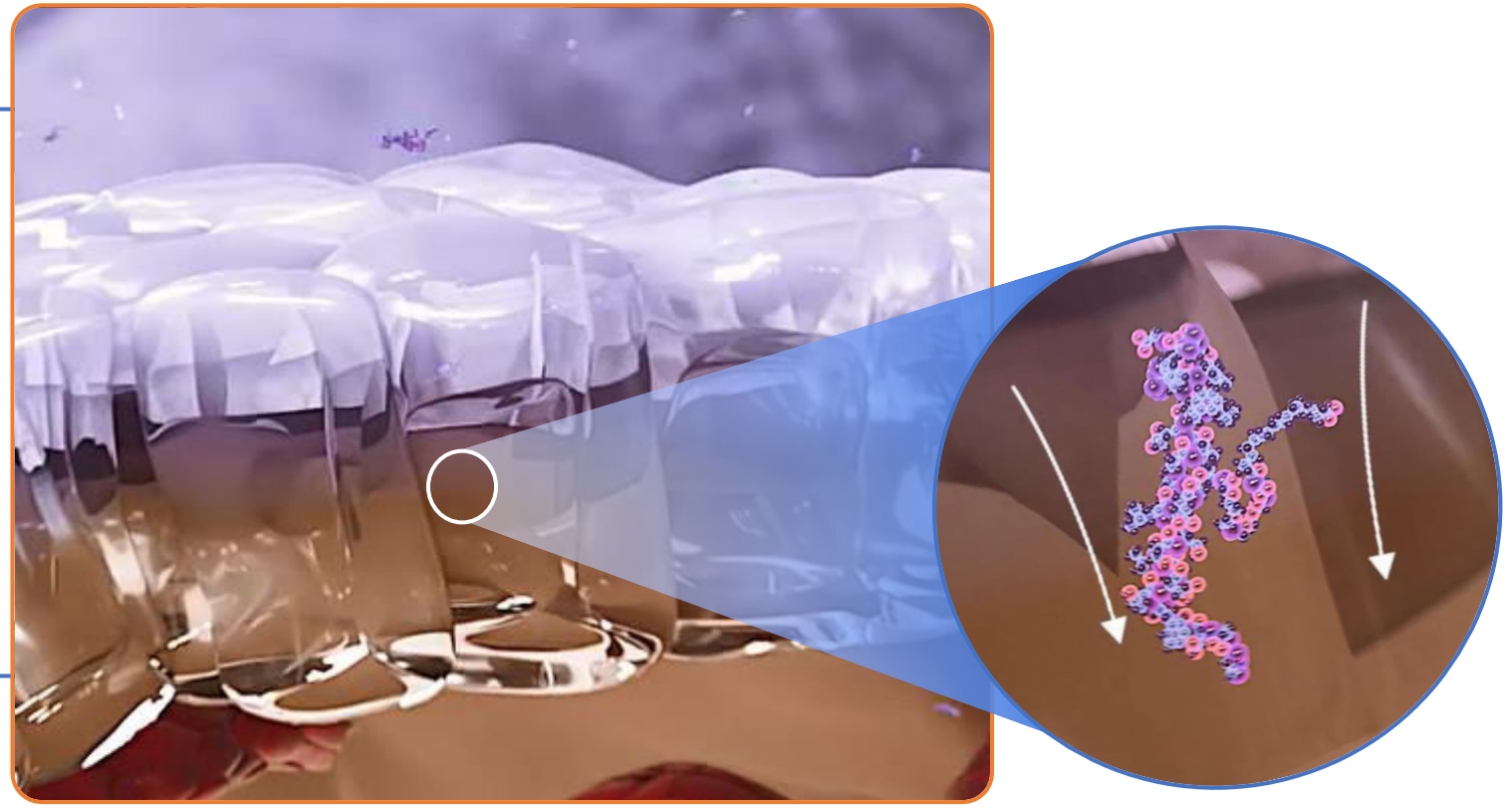
Buckley ST et al. Sci Transl Med 2018;10(467).

# Mechanism of absorption of oral semaglutide

## Transcellular absorption of semaglutide

**3**

- The effect of SNAC is strictly time- and concentration-dependent, and fully reversible
- Approx. 1% of semaglutide is absorbed, the rest is degraded in the GI tract



GI, gastrointestinal; SNAC, Sodium N-(8-(2-hydroxybenzoyl) amino) caprylate.

Buckley ST et al. *Sci Transl Med* 2018;10(467).

# Oral semaglutide

## PIONEER clinical trials

**24** Clinical pharmacology trials

**1** Phase 2 trial

**10** Phase 3a trials

**9,543**
**Subjects enrolled**

**Subjects exposed to oral semaglutide**

**~5,707**

# The PIONEER phase 3a clinical programme

## Diet and exercise

**PIONEER 1**

vs placebo

## Add-on to OAD

**PIONEER 2**

vs SGLT2i

**PIONEER 3**

vs DPP-4i

**PIONEER 4**

vs GLP-1RA/placebo

**PIONEER 7**

Flexible dose adjustment vs DPP-4i with extension

## Insulin users

**PIONEER 8**

Add-on to insulin (51 Indian subjects)

## Special populations

**PIONEER 5**

Renal impairment

**PIONEER 6**

CVOT (201 Indian subjects)

## Japanese trials

**PIONEER 9**

Japanese subjects (vs Liraglutide and placebo)

**PIONEER 10**

Japanese subjects (vs GLP-1RA Dulaglutide)

## Ongoing trial

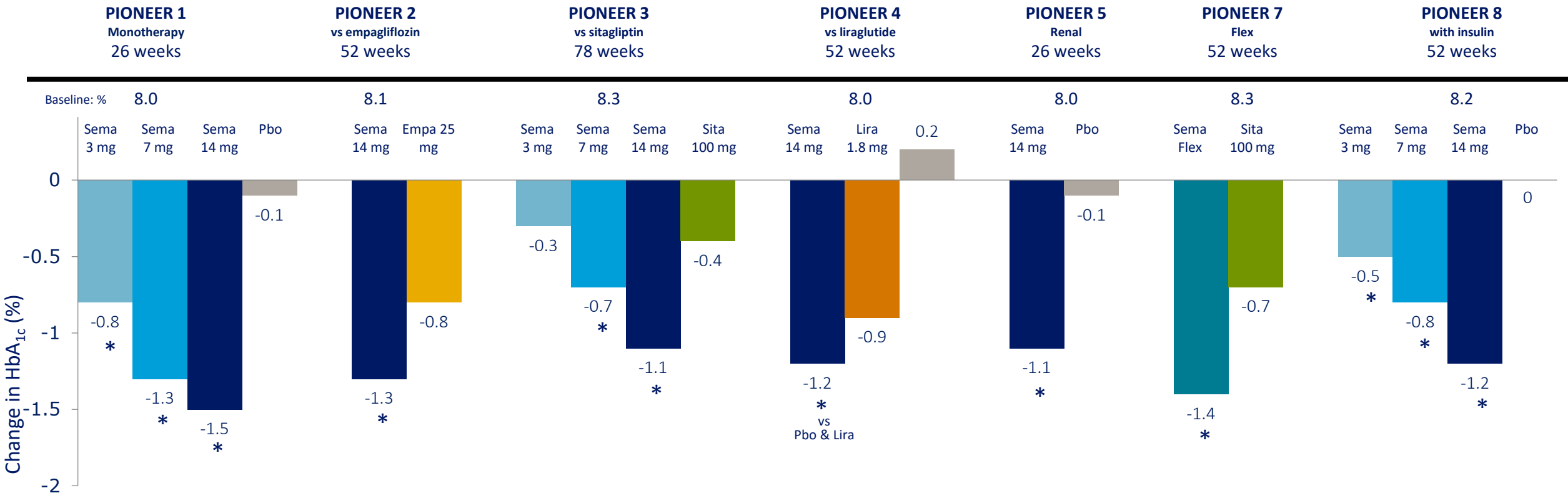
**SOUL (Superiority CVOT)** On-going

CVOT (≈788 Indian subjects)

Aroda VR. 2019; Rodbard H. 2019; Rosenstock J. 2019; Pratley R. 2019; Mosenzon O. 2019; Husain M. 2019; Pieber TR. 2019; Zinman B. 2019; Yamada Y. 2019; Yabe D. 2019.

# PIONEER 1–5, 7, 8

## CHANGE IN HBA1C AT THE END OF TREATMENT

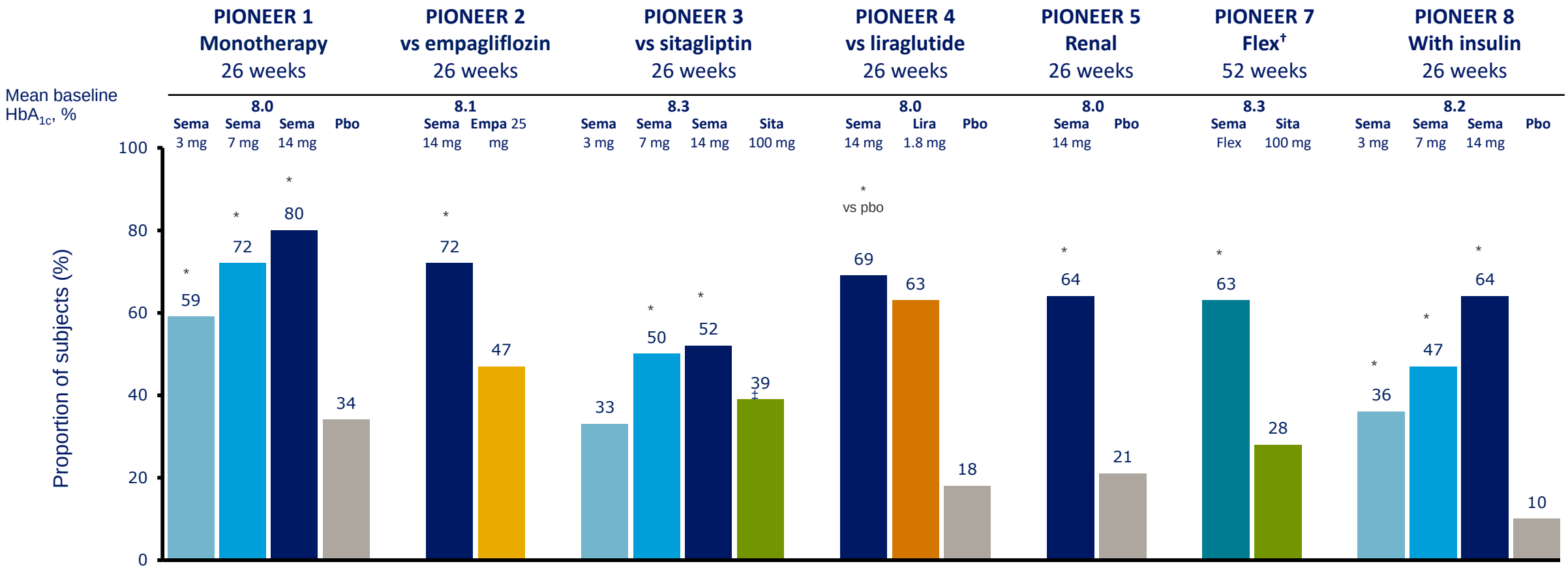



**Across Global PIONEER trials Oral Semaglutide achieved**
**HbA1c reduction up to 1.5%**

CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; Met, metformin; OAD, oral anti-diabetes drug; SGLT2i, sodium glucose co-transporter 2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.
Aroda VR. 2019; Rodbard H. 2019; Rosenstock J. 2019; Pratley R. 2019; Mosenzon O. 2019; Husain M. 2019; Pieber TR. 2019; Zinman B. 2019;

# PIONEER 1–5, 7, 8

## HBA1C <7.0% AT END OF TREATMENT

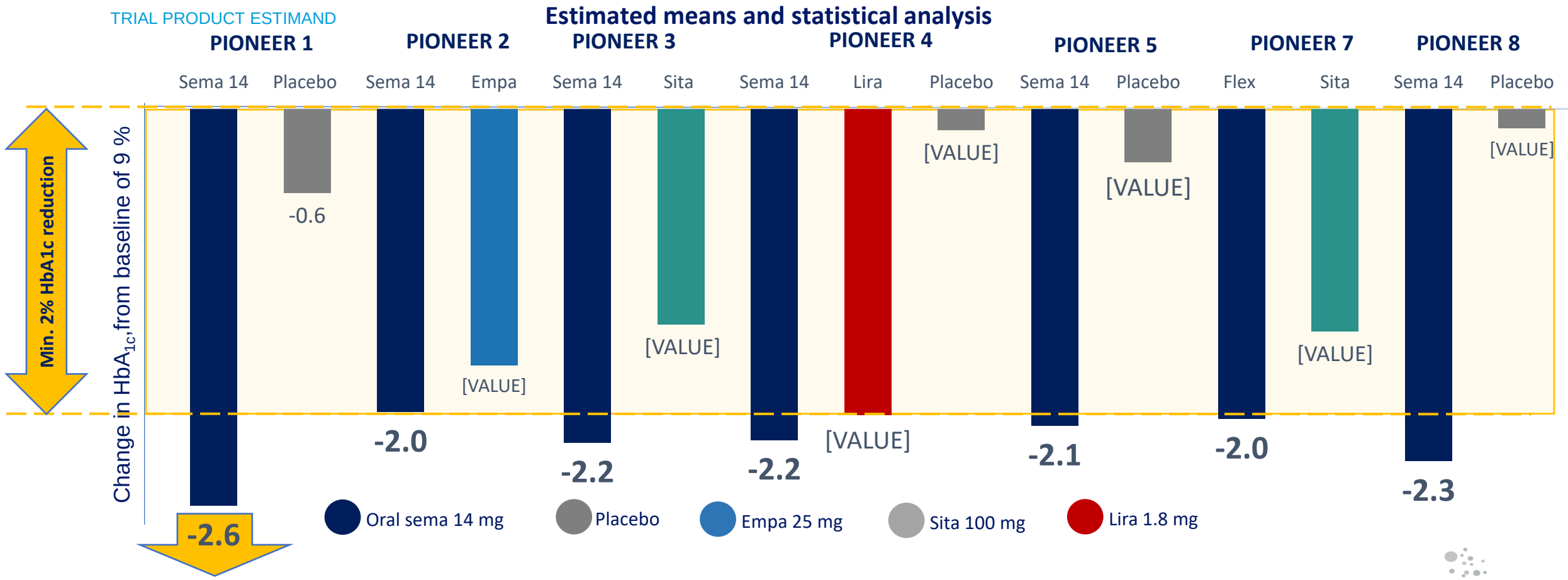



**Across PIONEER trials, ~7 out of 10 patients achieve HbA1c<7% with Oral Semaglutide**

*p<0.05 for odds of achieving $HbA_{1c}$ <7.0% with oral semaglutide vs placebo or active comparator. †Primary endpoint in PIONEER 7, subjects achieving $HbA_{1c}$ <7.0%. ‡p<0.05 for odds of achieving $HbA_{1c}$ <7.0% with sitagliptin 100 mg versus oral semaglutide 3 mg. Flex, flexible; Empa, empagliflozin; Lira, liraglutide; Pbo, placebo; Sema, semaglutide; Sita, sitagliptin. Aroda VR, et al. *Diabetes Care* 2019;42:1724–32; Rodbard HW, et al. *Diabetes Care* 2019;42:2272–2281; Rosenstock J, et al. *JAMA* 2019;321:1466–80; Pratley R, et al. *Lancet* 2019;394:39–50; Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:515–27; Pieber TR, et al. *Lancet Diabetes Endocrinol* 2019;7:528–39; Zinman B et al. *Diabetes Care* 2019;42:2262–2271.

# Change in $HbA_{1c}$ from baseline >9%

## ORAL SEMAGLUTIDE 14 MG POST HOC ANALYSIS



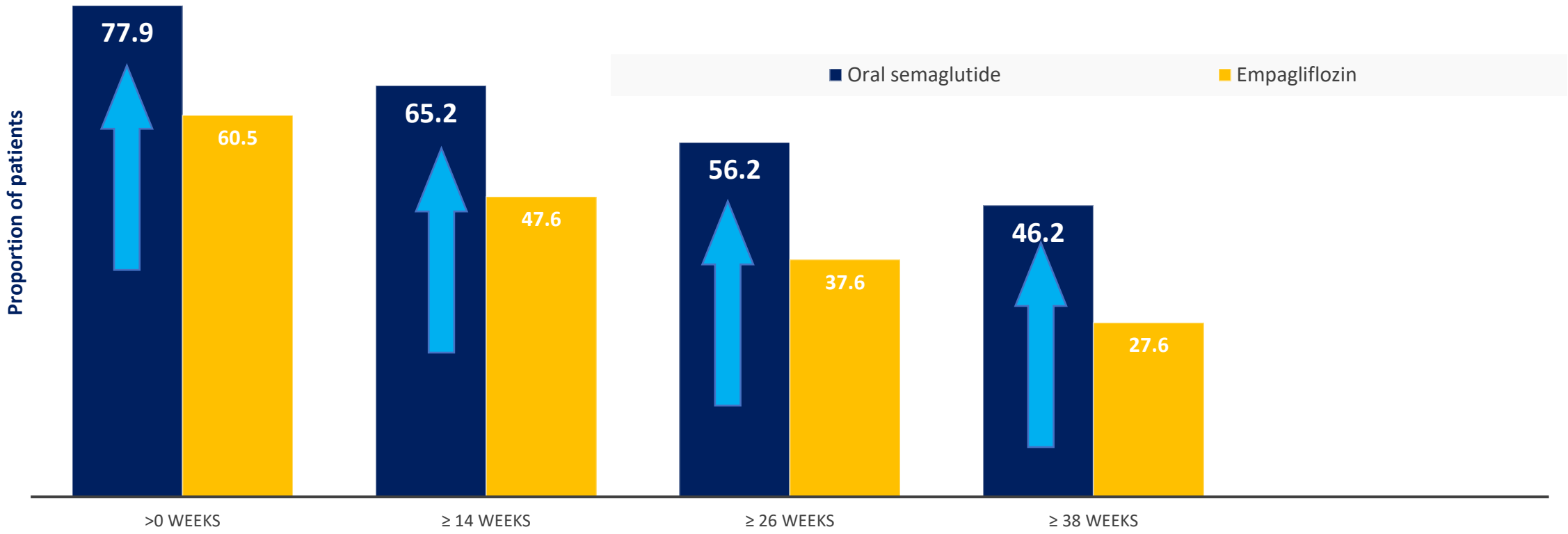

**In Post-Hoc analysis with baseline HbA1c >9% oral semaglutide resulted in HbA1c reduction up to 2.6%**

*J. Meier et al.* EFFICACY OF ORAL SEMAGLUTIDE ACCORDING TO BASELINE HBA1C: AN EXPLORATORY SUBGROUP ANALYSIS OF THE PIONEER TRIAL PROGRAMME. Diabetes Technology & Therapeutics. Feb 2020.A-1-A-250.http://doi.org/10.1089/dia.2020.2525.abstracts **Published in** Volume: 22 Issue S1: February 18, 2020

# PIONEER 2 exploratory analysis

## TIME SPENT IN GLYCEMIC CONTROL

### Oral Semaglutide Versus Empagliflozin

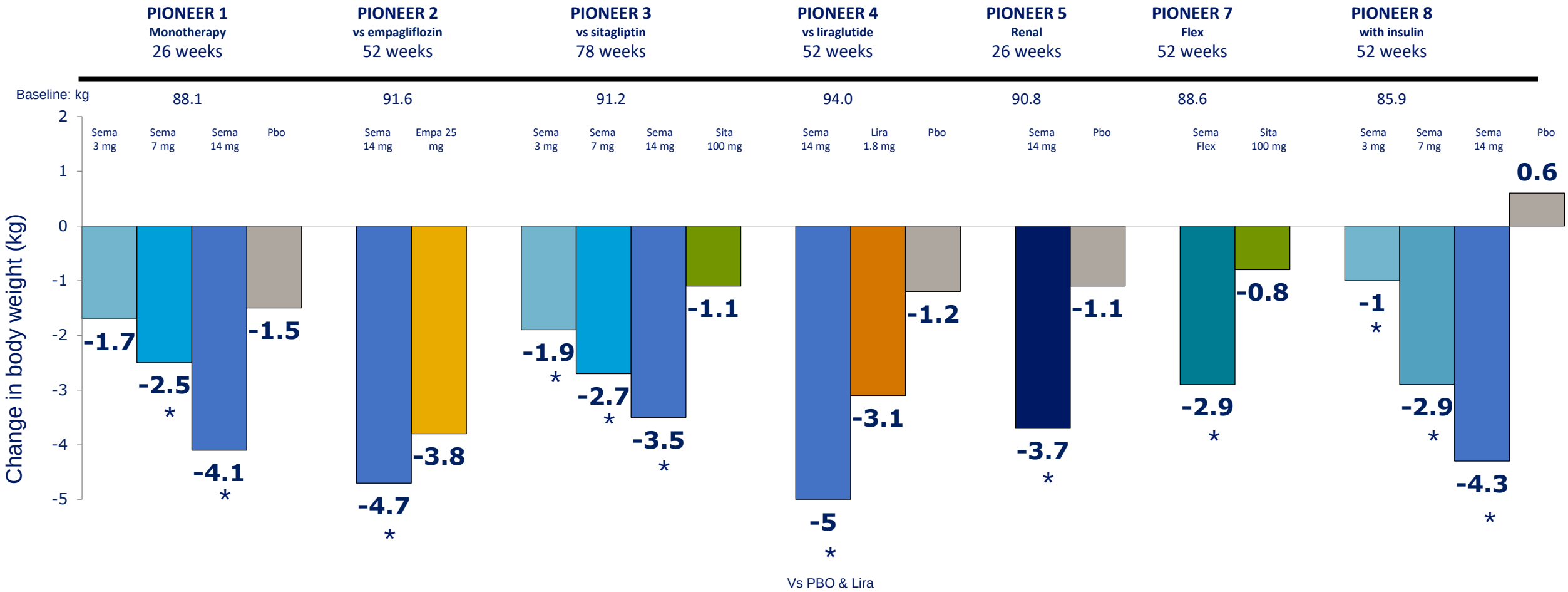



**40% greater time spent in glycemic control with oral semaglutide vs empagliflozin**

Rosenstock, et al Time Spent in Glycemic Control after Initiating Treatment with Oral Semaglutide vs. Empagliflozin: An Exploratory Analysis of the PIONEER 2 Trial. Poster presented at: 81st Scientific Sessions of the American Diabetes Association. June 25 - 29, 2021

# PIONEER 1–5, 7, 8

## CHANGE IN BODY WEIGHT – END OF TREATMENT



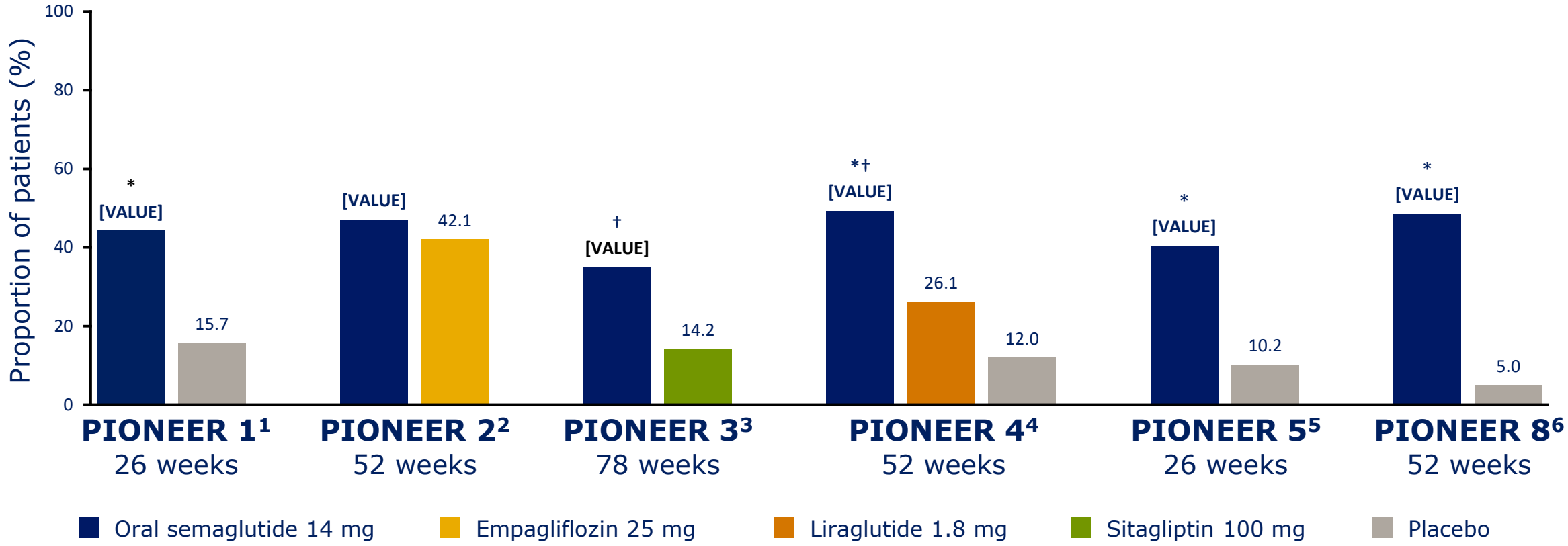

**Across Global PIONEER trials Oral Semaglutide achieved**
**Weight reduction up to 5 kg**

Disclaimer: Oral semaglutide is not approved for weight reduction

CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; Met, metformin; OAD, oral anti-diabetes drug; SGLT2i, sodium glucose co-transporter 2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

Aroda VR. 2019; Rodbard H. 2019; Rosenstock J. 2019; Pratley R. 2019; Mosenzon O. 2019; Husain M. 2019; Pieber TR. 2019; Zinman B. 2019; Yamada Y. 2019; Yabe D. 2019.

# Proportions of patients achieving a body wt. loss of ≥5%

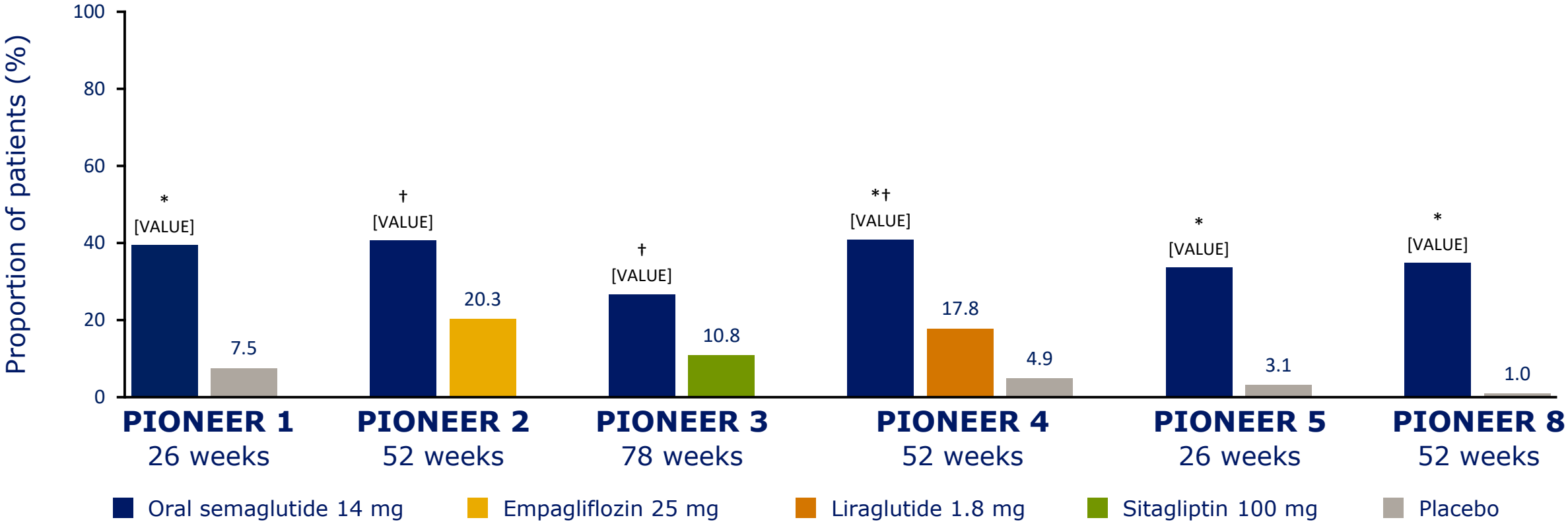



**In Post-Hoc analysis significantly more number of patient achieved wt. loss ≥5% with oral semaglutide 14mg compared to placebo & comparators**

Data are observed proportions for the trial product estimand (on trial product without rescue medication). *p<0.0001 for the EOR with oral semaglutide 14 mg vs placebo.
†p<0.0001 for the EOR with oral semaglutide 14 mg vs the active comparator. EOR, estimated odds ratio.
1. Aroda VR, et al. Diabetes Care. 2019;42:1724–32; 2. Rodbard H, et al. Diabetes Care. 2019;42:2272–81; 3. Rosenstock J, et al. JAMA. 2019;321:1466–80;
4. Pratley R, et al. Lancet. 2019;394:39–50; 5. Mosenzon O, et al. Lancet Diabetes Endocrinol. 2019;7:515–27; 6. Zinman B, et al. Diabetes Care. 2019;42:2262–71.

# Proportions of patients achieving

## HBA1C REDUCTION OF ≥1% AND BODY WEIGHT LOSS OF ≥5%



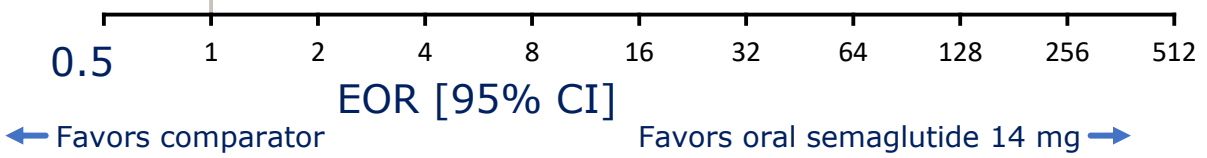

**In Post-Hoc analysis with oral semaglutide 14mg higher proportion of pt. achieved HbA1c reduction of ≥1% and wt. loss ≥5% compared to placebo & comparators**

Data are observed proportions for the trial product estimand (on trial product without rescue medication). Whether a patient achieved a weight loss of ≥5% was analysed as a separate endpoint in the PIONEER trials; these data are presented on the previous slide. Whether a patient achieved an $HbA_{1c}$ reduction of ≥1% was only analysed as part of a composite endpoint in the PIONEER trials and so these data are not reported.
*p<0.0001 for the EOR with oral semaglutide 14 mg vs placebo. †p<0.0001 for the EOR with oral semaglutide 14 mg vs the active comparator.
EOR, estimated odds ratio. Dungan KM, et al. Presented at the American Diabetes Association 80th Scientific Sessions Virtual Meeting, June 12–16, 2020. Poster 964-P.

# Odds of achieving

## HBA1C REDUCTION OF ≥1% AND BODY WEIGHT LOSS OF ≥5%

| | | | EOR [95% CI] | P value |
|---|---|---|---|---|
| **PIONEER 1** | vs placebo | 9.5 X | 9.61 [4.66, 19.85] | <0.0001 |
| **PIONEER 2** | vs empagliflozin 25 mg | 2.5 X | 2.62 [1.85, 3.70] | <0.0001 |
| **PIONEER 3** | vs sitagliptin 100 mg | ~4 X | 3.87 [2.51, 5.95] | <0.0001 |
| **PIONEER 4** | vs liraglutide 1.8 mg | 3 X | 3.10 [2.02, 4.73] | <0.0001 |
| | vs placebo | ~19 X | 18.93 [6.74, 53.20] | <0.0001 |
| **PIONEER 5** | vs placebo | ~16 X | 15.85 [5.58, 45.03] | <0.0001 |
| **PIONEER 8** | vs placebo | ~55 X | 55.19 [8.41, 362.40] | <0.0001 |

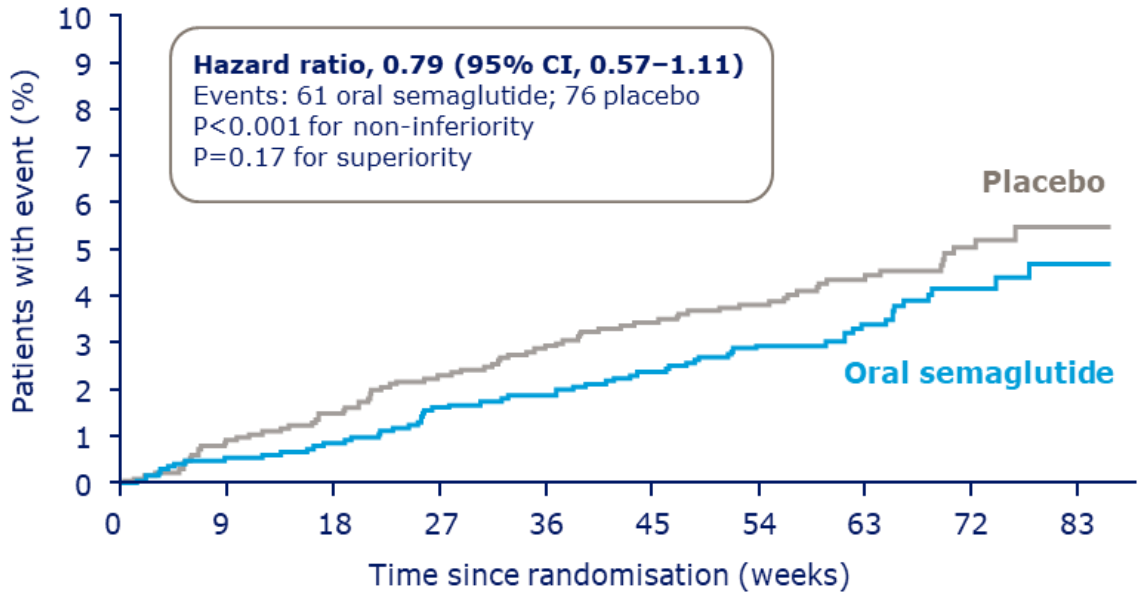



**With Oral semaglutide 14mg odds were significantly higher to achieved HbA1c reduction of ≥1% and wt. loss ≥5% compared to placebo & comparators**

Data are for the trial product estimand (on trial product without rescue medication).
CI, confidence interval; EOR, estimated odds ratio. Dungan KM, et al. Presented at the American Diabetes Association 80th Scientific Sessions Virtual Meeting, June 12–16, 2020. Poster 964-P.

# Oral semaglutide results from CV outcomes trial

## Time to first occurrence of CV death, non-fatal MI or non-fatal stroke




## PIONEER 6 overall summary

**Population**

Age ≥50 years with established CV disease

**OR**

Age ≥60 years with at least one CV risk factor

**High retention and follow-up**

99.7% completed the study*

Vital status known for 100% of patients

**Primary outcome**

CV death, non-fatal MI or non-fatal stroke

**CV safety established**

**21%**

**Non-significant risk reduction vs placebo**

**$HbA_{1c}$ and body weight**

**significantly reduced vs placebo**

**Overall AE profile**

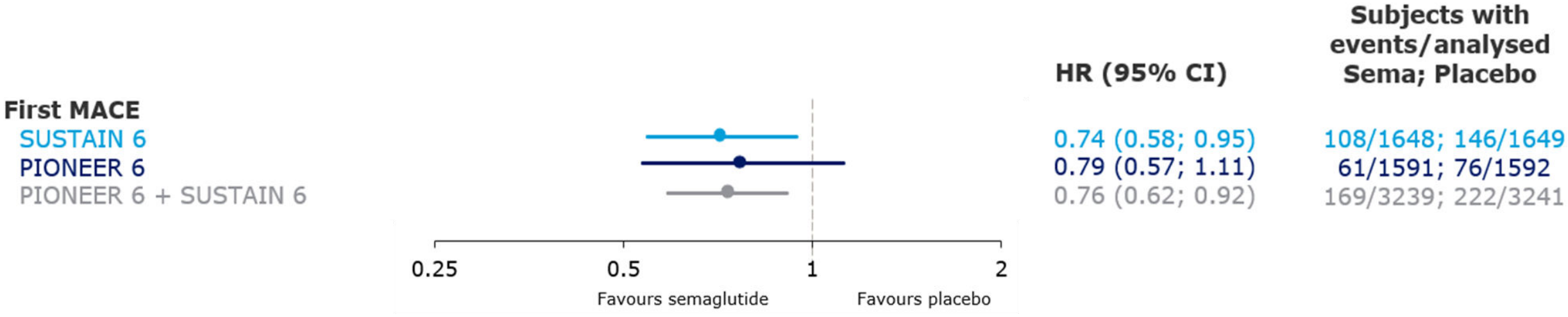
Like any other GLP-1 receptor agonists

**Oral semaglutide achieved its primary endpoint of MACE reduction vs placebo with 21% non-significant risk reduction**

*Cumulative incidence function shown for 1st event adjudication committee-confirmed CV death, non-fatal MI and non-fatal stroke using 'in-trial' data from subjects in the full analysis set. *Trial completers are defined as subjects that either attend the last follow-up visit or who die during the trial. AE, adverse event; CI, Confidence interval; CV, cardiovascular; GLP-1, glucagon-like peptide-1; MI, myocardial infarction. Source: Husain et al. N Engl J Med 2019381:841–51*

# Pooled cardiovascular outcomes data for

## ORAL AND SUBCUTANEOUS SEMAGLUTIDE




**In SUSTAIN and PIONEER combined, semaglutide showed consistent effects on MACE with 24% risk reduction versus comparators across varying CV risk**

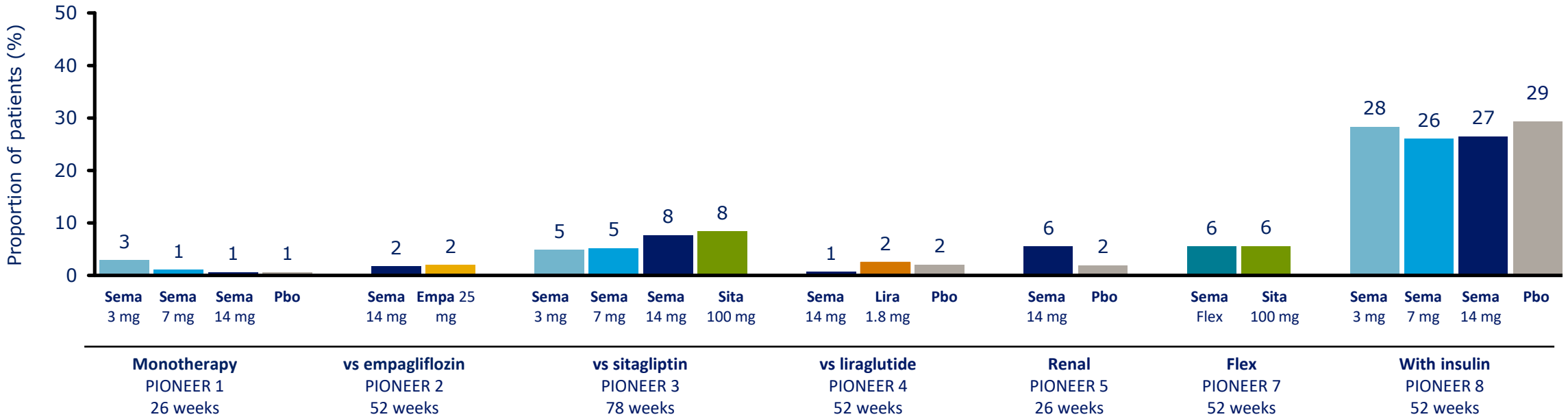
| SUSTAIN-6[1] | PIONEER-6[2] |
|---|---|
| Both event and time driven | **Only event-driven** |
| 254 CV events | 137 CV events |
| median observation time= 2.1 years | median observation time = **16 months** |
| HR of MACE reduction = 0.74 | HR of MACE reduction = 0.79 |

**Even though similar hazard ratios, PIONEER -6 achieved non-inferiority level for CV safety, while SUSTAIN-6 also could prove superiority for MACE reduction due to difference in study design**

CI: Confidence interval; HR: Hazard ratio; MACE: Major adverse cardiovascular event; Sema: semaglutide Cardiovascular death includes undetermined cause of death. Estimated hazard ratios and corresponding confidence intervals are from separate Cox proportional hazards models with treatment as fixed factor and stratified by trial and stratification factors. Reference: Husain et al. Diabetes Obes Metab. 2020;22:442–451.

*sub-cutaneous Semaglutide is not approved/marketed in India

# Proportion of patients with severe or blood glucose-confirmed symptomatic hypoglycaemia

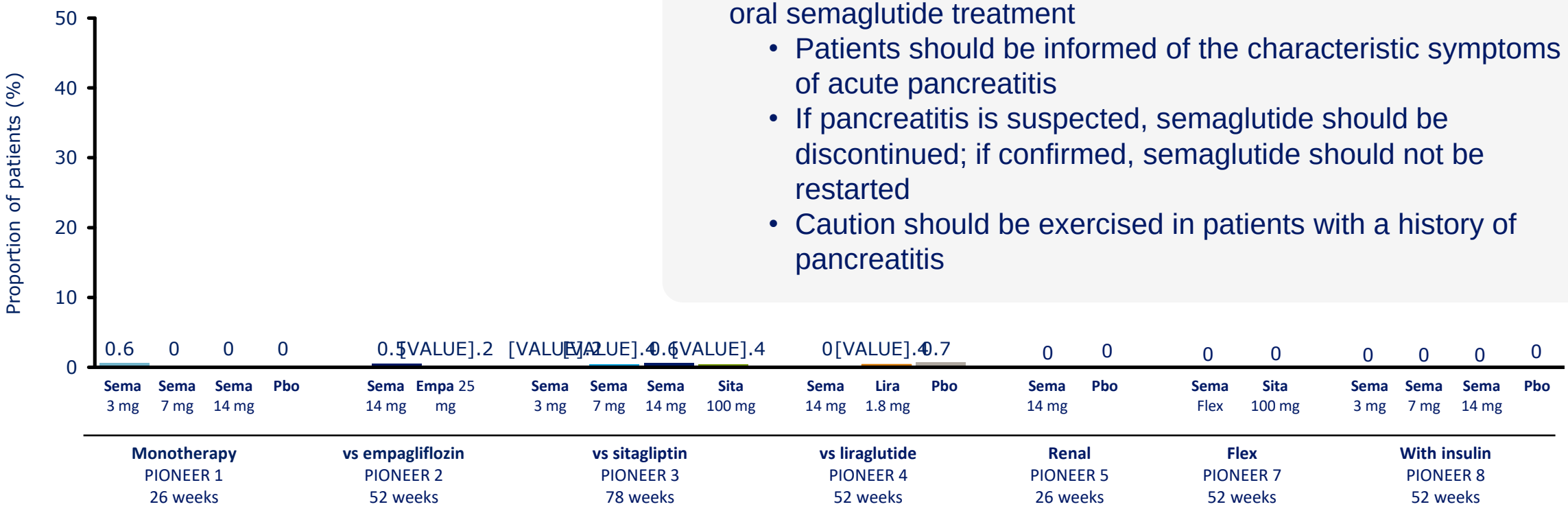



- Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia
- The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide


Aroda VR, et al. Diabetes Care 2019;42:1724–1732;Rodbard H et al. Diabetes Care 2019;42:2272–2281; Rosenstock J et al. JAMA 2019;321:1466–1480; Pratley R et al. Lancet 2019;394:39–50; Mosenzon O et al. Lancet Diabetes Endocrinol 2019;7:515–527; Pieber TR et al. Lancet Diabetes Endocrinol 2019;7:528–539; Zinman B et al. Diabetes Care 2019;42:2262–2271; Rybelsus® European summary of product characteristics 2020

# Proportion of patients with pancreatitis

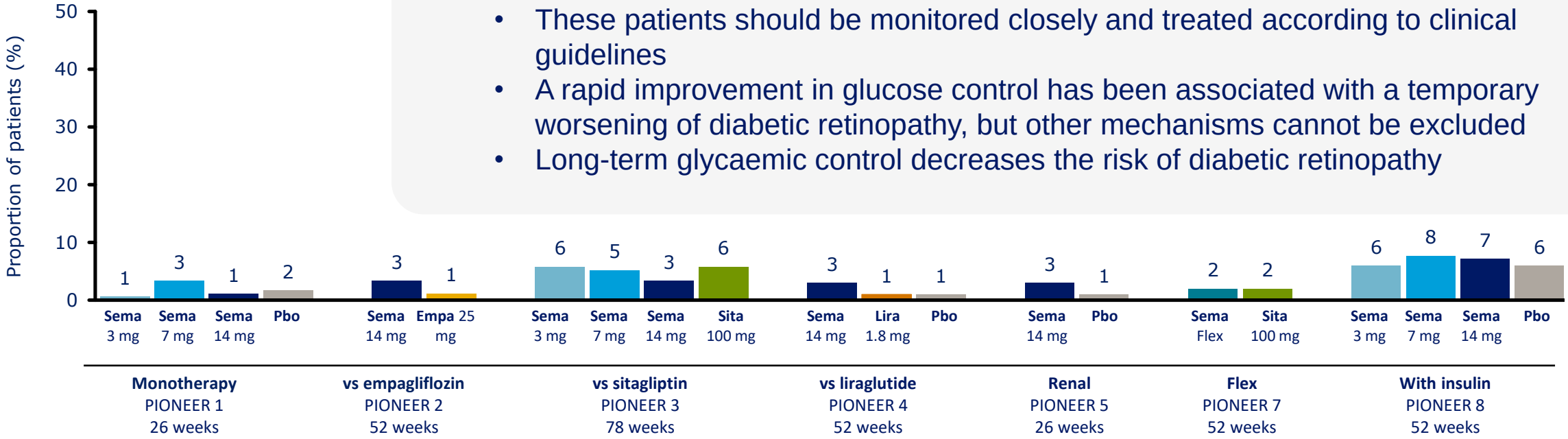
- There appears to be a very low risk of pancreatitis associated with oral semaglutide treatment
  - Patients should be informed of the characteristic symptoms of acute pancreatitis
  - If pancreatitis is suspected, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted
  - Caution should be exercised in patients with a history of pancreatitis




Aroda VR, et al. Diabetes Care 2019;42:1724–1732;Rodbard H et al. Diabetes Care 2019;42:2272–2281; Rosenstock J et al. JAMA 2019;321:1466–1480; Pratley R et al. Lancet 2019;394:39–50; Mosenzon O et al. Lancet Diabetes Endocrinol 2019;7:515–527; Pieber TR et al. Lancet Diabetes Endocrinol 2019;7:528–539; Zinman B et al. Diabetes Care 2019;42:2262–2271; Rybelsus® European summary of product characteristics 2020

# Proportion of patients with diabetic retinopathy

- **The incidence of diabetic retinopathy was like that with comparators, including placebo**
  - Caution should be exercised when using semaglutide in patients with diabetic retinopathy
  - These patients should be monitored closely and treated according to clinical guidelines
  - A rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded
  - Long-term glycaemic control decreases the risk of diabetic retinopathy




Aroda VR, et al. Diabetes Care 2019;42:1724–1732;Rodbard H et al. Diabetes Care 2019;42:2272–2281; Rosenstock J et al. JAMA 2019;321:1466–1480; Pratley R et al. Lancet 2019;394:39–50; Mosenzon O et al. Lancet Diabetes Endocrinol 2019;7:515–527; Pieber TR et al. Lancet Diabetes Endocrinol 2019;7:528–539; Zinman B et al. Diabetes Care 2019;42:2262–2271; Rybelsus® European summary of product characteristics 2020

# Oral semaglutide in special population

**No dose adjustment recommended** regardless of renal or hepatic impairment[1–3*]

**No dose adjustment recommended** in elderly patients[3]

**Low risk of hypoglycaemia** across the PIONEER trials[4–10]

1. Granhall C et al. Clin Pharmacokinet 2018;57:1571–1580; 2. Bækdal TA et al. J Clin Pharmacol 2018;58:1314–1323; 3. Rybelsus® European summary of product characteristics; 4. Aroda VR et al. Diabetes Care 2019;42:1724–1732; 5. Rodbard H et al. Diabetes Care 2019;42:2272–2281; 6. Rosenstock J et al. JAMA 2019;321:1466–1480; 7. Pratley R et al. Lancet 2019;394:39–50; 8. Mosenzon O et al. Lancet Diabetes Endocrinol 2019;7:515–527; 9. Pieber TR et al. Lancet Diabetes Endocrinol 2019;7:528–539; 10. Zinman B et al. Diabetes Care 2019;42:2262–2271

# Summary: oral semaglutide

## PIONEER 1, 2, 3, 4, 5, 6, 7 & 8

### $HbA_{1c}$

**Oral semaglutide superior vs:**

- Empagliflozin
- Sitagliptin

**Non-inferior vs:**

- Liraglutide

### Weight

**Oral semaglutide superior vs:**

- Sitagliptin
- Liraglutide
- Empagliflozin$^{(EoT)}$

### Cardiovascular safety

Confirmed for oral semaglutide in PIONEER 6, showing a 21% non-significant reduction in MACE in favour of oral semaglutide compared with placebo

### End of trial

Oral semaglutide demonstrated significant greater $HbA_{1c}$ and weight reductions vs sitagliptin, empagliflozin and liraglutide

### Overall safety

Oral semaglutide was well-tolerated with a safety profile consistent with the GLP-1RA class. The most common adverse event was mild to moderate nausea

**Efficacy was established when given early in therapy, late in therapy and regardless of renal or hepatic impairment**

GLP-1RA, glucagon-like peptide 1 receptor agonist; MACE, major adverse cardiovascular event; EoT: End of trial.

# Agenda

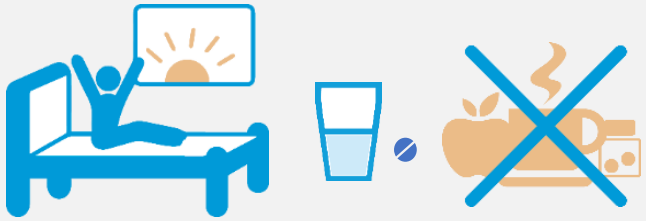
- Role of GLP-1 RAs in management of T2DM
- PIONEERing a new era: Triumphing targets with Oral Semaglutide
- PIONEERing management in routine clinical practice

# How oral semaglutide should be administered ?

## DOSING INSTRUCTIONS ARE DESIGNED TO OPTIMISE ABSORPTION & BE SIMPLE FOR PATIENTS

**Take when you wake on an empty stomach**

Wake up and take your semaglutide tablet straight away with up to half a glass of water (approximately 120 mL/4 fl oz)



**Then wait**

Wait at least **30 minutes** before eating, drinking or taking any other oral medication


**Schedule**

**3 mg** (starting dose) | **7 mg** (treatment dose) | **14 mg** (treatment dose if further glycaemic control needed)

Start — Month 1 — Month 2

Dose escalation

**Advise patients that if they miss a dose, they should skip the missed dose and take the next dose as scheduled the next day**

*Used in Phase 2 and Phase 3a (PIONEER) programme.*

# Ideal patients for initiation of oral semaglutide

| | |
|---|---|
| *Patients taking one or more oral antihyperglycemic agent (including metformin) with inadequate glycemic control* | • Appropriate agent for the second-line setting, after failure of metformin |
| *Patients for whom weight loss would be beneficial* | ▪ Superior weight reduction than comparators<br>▪ Reasonable to consider for patients who would benefit from weight loss |
| *Patients in whom hypoglycemia is concern* | ▪ Overall low risk of hypoglycemia,<br>▪ Similar to empagliflozin, sitagliptin, and GLP-1RA |
| *Patients already receiving an injectable GLP-1RA and not reaching glycemic targets* | • first explore challenges related to adherence<br>• consider switching to a tablet formulation |
| *Patients with established CVD or at high CV risk* | • High Risk/established ASCVD patient: Patient preference for oral therapy than SC |
| *Patients with established renal or hepatic dysfunction* | • No dose adjustments are recommended in patients with hepatic or renal dysfunction |
| *Older patients* | • Patient age does not appear to affect efficacy or safety of oral semaglutide |

Stephen A. Brunton, Ofri Mosenzon & Eugene E. Wright Jr (2020) Integrating oral semaglutide into clinical practice in primary care: for whom, when, and how?, Postgraduate Medicine, 132:sup2, 48-60

# Summary

GLP-1 RAs are among the most effective medications for T2D which have been shown to reduce HbA1C, body weight, composite outcomes and even pill burden

Oral semaglutide is a scientific breakthrough in innovation to bring efficacy of GLP-1 RAs in convenient oral formulation

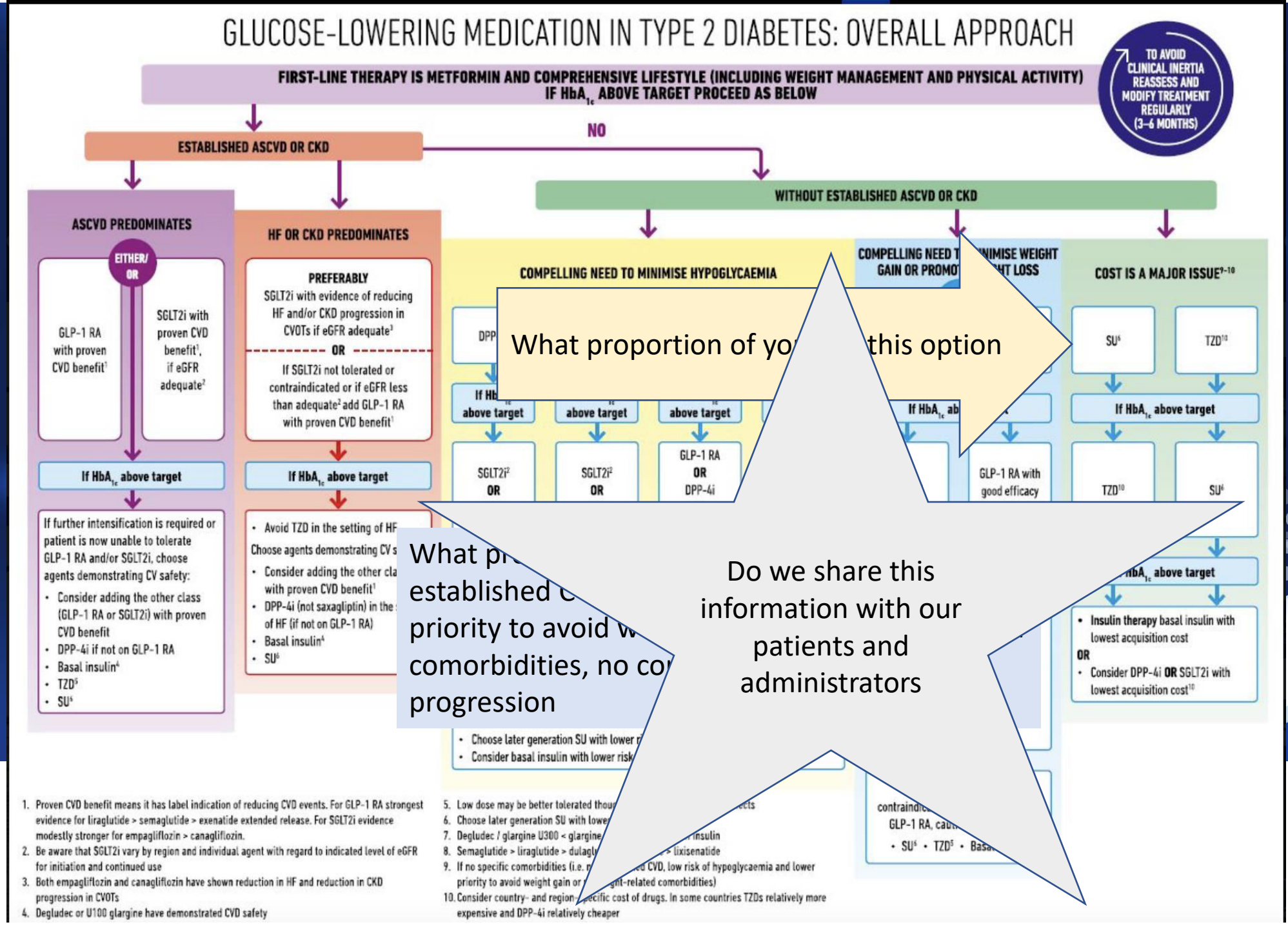
Across Global PIONEER trials Oral Semaglutide proven its efficacy and achieved HbA1c reduction up to 1.5% and weight reduction up to 5 Kg

Oral semaglutide has been found to reduce HbA1c more than an SGLT2i & DPP4i when added to 1 -2 oral drugs, and reduces HbA1c when added to insulin-based therapy

In patients with baseline HbA1c >9% oral semaglutide resulted in HbA1c reduction up to 2.6%

Oral semaglutide has proven CV safety in PIONEER-6 with a strong potential for CV death and all cause death reduction and a larger SOUL trial, to evaluate the long-term cardiovascular benefit of oral semaglutide is ongoing

Efficacy of oral semaglutide was established when given early in therapy, late in therapy and regardless of renal or hepatic impairment




Proven CVD benefit Liraglutide>semaglutide>exenatide extended release, empagliflozin>canagliflozin

Empagliflozin and canagliflozin – reduction in HF and CKD progression

GLP-1 RA for weight loss semaglutide>liraglutide>dulaglutide>exenatide>lixisenatide

# Thank You