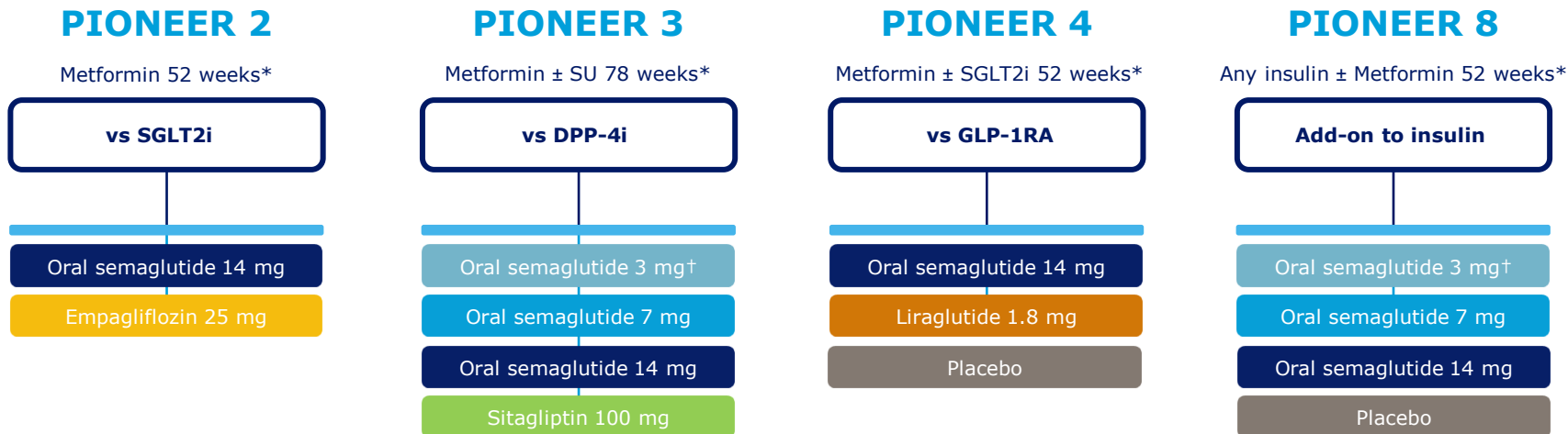


Direct comparisons between trials should not be made due to differences in trial designs

Highlighted trials of the PIONEER programme



*Time to primary endpoint: 26 weeks for PIONEER 2, 3, 4, and 8. †Please note that 3 mg is not a licensed maintenance dose for oral semaglutide.

DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; PIONEER, peptide innovation for early diabetes treatment; SGLT2i, sodium glucose co-transporter-2 inhibitor; SU, sulphonylurea. Rodbard HW et al. *Diabetes Care* 2019;42:2272–2281; Rosenstock J et al. *JAMA* 2019;321:1–15; Pratley R et al. *Lancet* 2019. doi: 10.1016/S0140-6736(19)31271-1; Zinman B et al. *Diabetes Care* 2019;42:2262–2271.

Estimands in the PIONEER programme

Treatment policy estimand

Evaluates the treatment effect for all randomised subjects **regardless of trial product discontinuation** and use of rescue medication
This was **the primary estimand** in the trials

Trial product estimand

Evaluates the treatment effect for all randomised subjects under the assumption that all subjects **remained on trial product** for the entire planned duration of the trial and did not use rescue medication

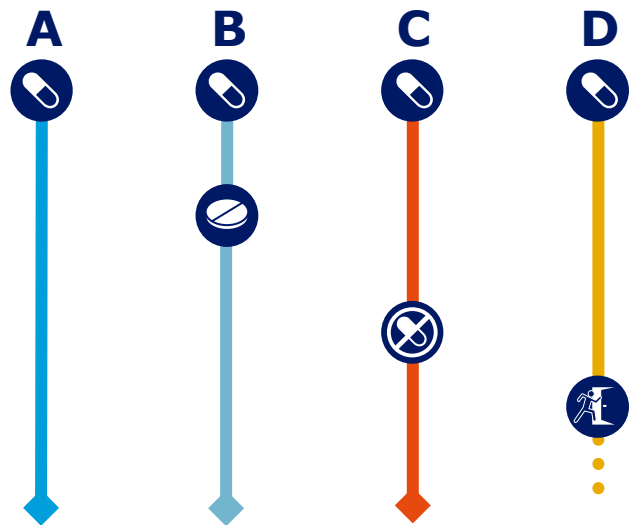
Trial product discontinuation and initiation of rescue medication are accounted for by the treatment policy strategy for the treatment policy estimand and by the hypothetical strategy for the trial product estimand as defined in draft ICH E9 (R1). PIONEER, peptide innovation for early diabetes treatment.

Food and Drug Administration 2017. E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM582738.pdf>. Accessed July 2019.

Estimands in the PIONEER programme

TREATMENT POLICY ESTIMAND:

What is the treatment effect in the target population regardless of trial product discontinuation or use of rescue medication?



Patient A
Completes treatment

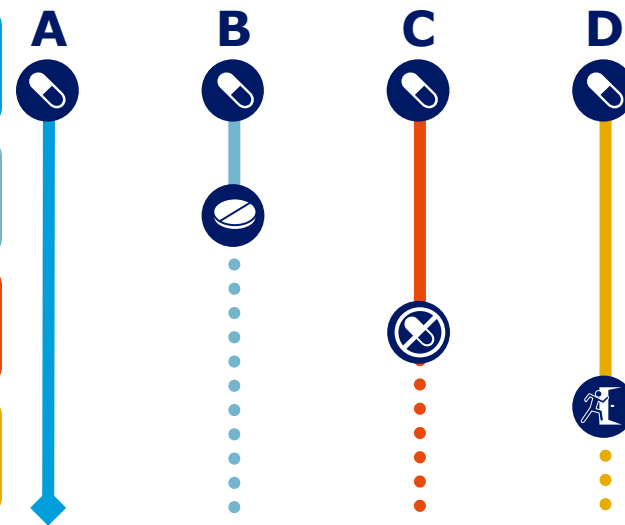
Patient B
Initiates rescue
medication

Patient C
Discontinues trial
product

Patient D
Withdraws

TRIAL PRODUCT ESTIMAND:

What is the treatment effect in the target population had all patients remained on trial product and did not use rescue medication?



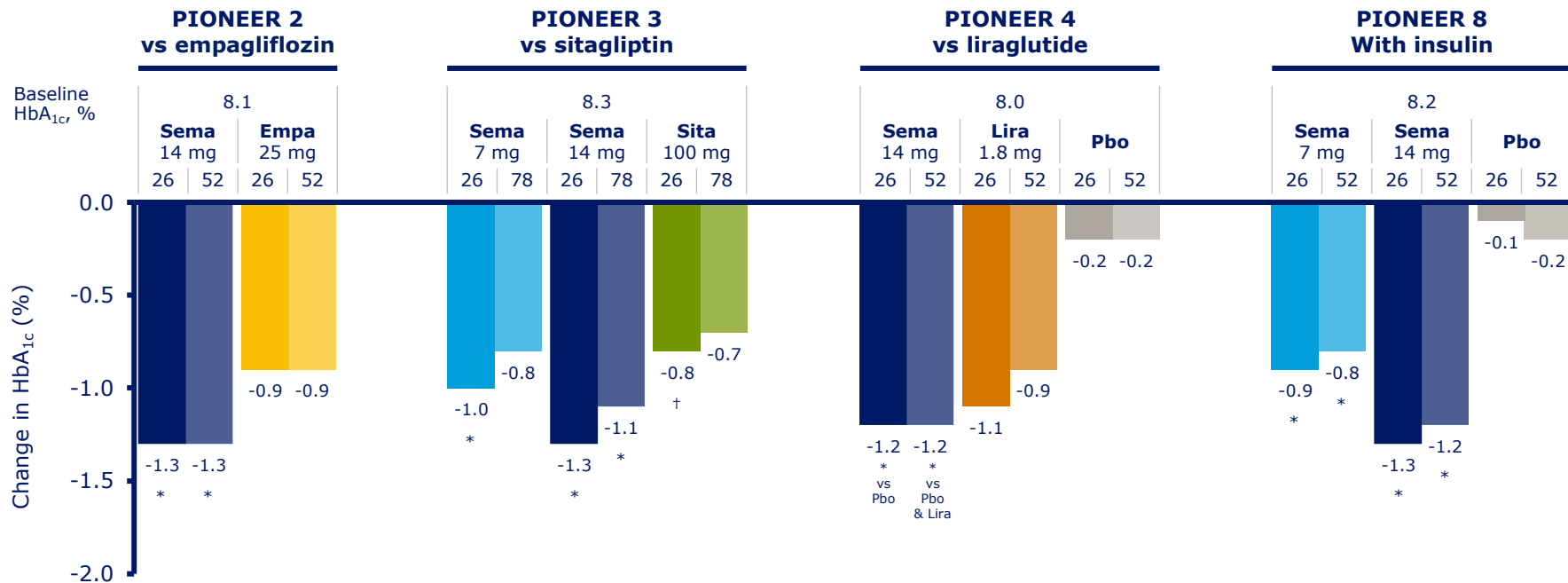
Statistical analysis: mixed model for repeated measures assuming subjects with missing data behave similarly to other subjects in the same treatment group

Statistical analysis: pattern mixture model with multiple imputations to handle missing data. Imputations groups defined by trial product and treatment status at timepoint for evaluation

Direct comparisons between trials should not be made due to differences in trial designs

PIONEER 2, 3, 4 and 8

CHANGE IN HbA_{1c} OVER TIME – TREATMENT POLICY ESTIMAND



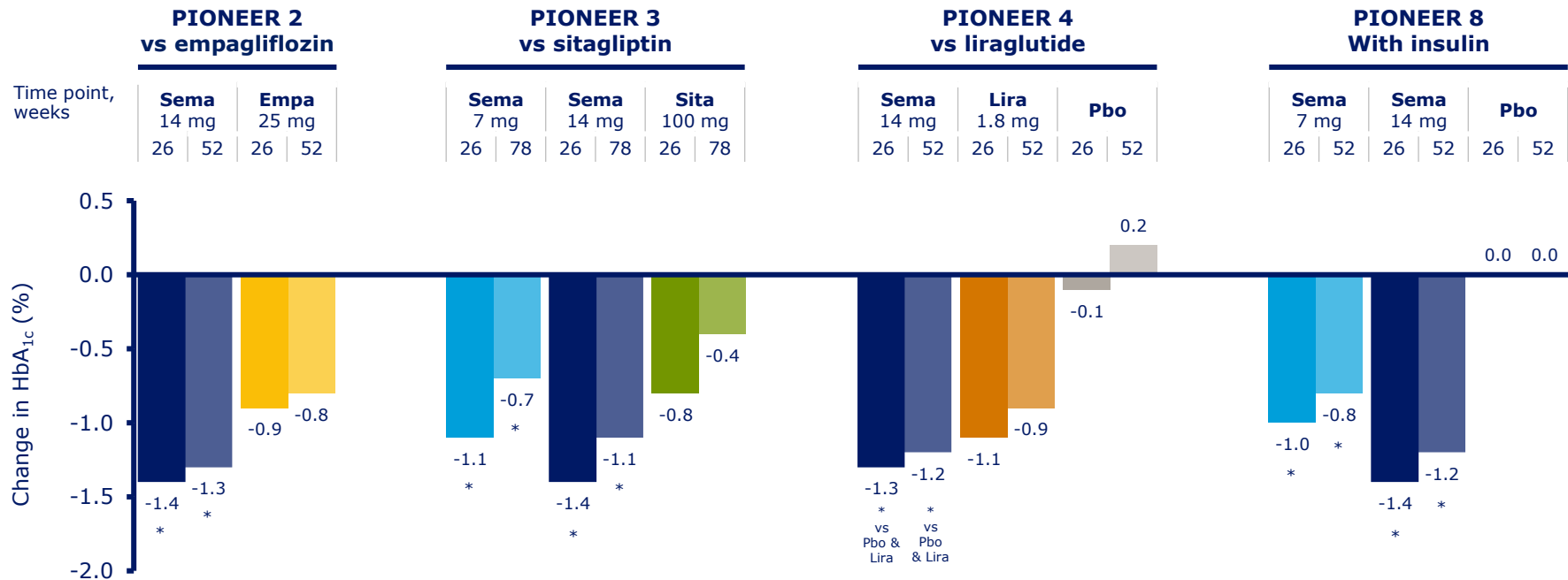
*Statistically significantly greater compared with placebo or active comparator. †Statistically significantly in favour of sitagliptin 100 mg compared with oral semaglutide 3 mg.

Empa, empagliflozin; HbA_{1c}, glycated haemoglobin; Lira, liraglutide; Pbo, placebo; PIONEER, peptide innovation for early diabetes treatment; Sema, semaglutide; Sita, sitagliptin. Rodbard HW et al. *Diabetes Care* 2019;42(12):2272–2281; Rosenstock J et al. *JAMA* 2019;321:1466–80; Pratley R et al. *Lancet* 2019;394:39–50; Zinman B et al. *Diabetes Care* 2019;42(12):2262–2271.

Direct comparisons between trials should not be made due to differences in trial designs

PIONEER 2, 3, 4, and 8

CHANGE IN HbA_{1c} OVER TIME – TRIAL PRODUCT ESTIMAND



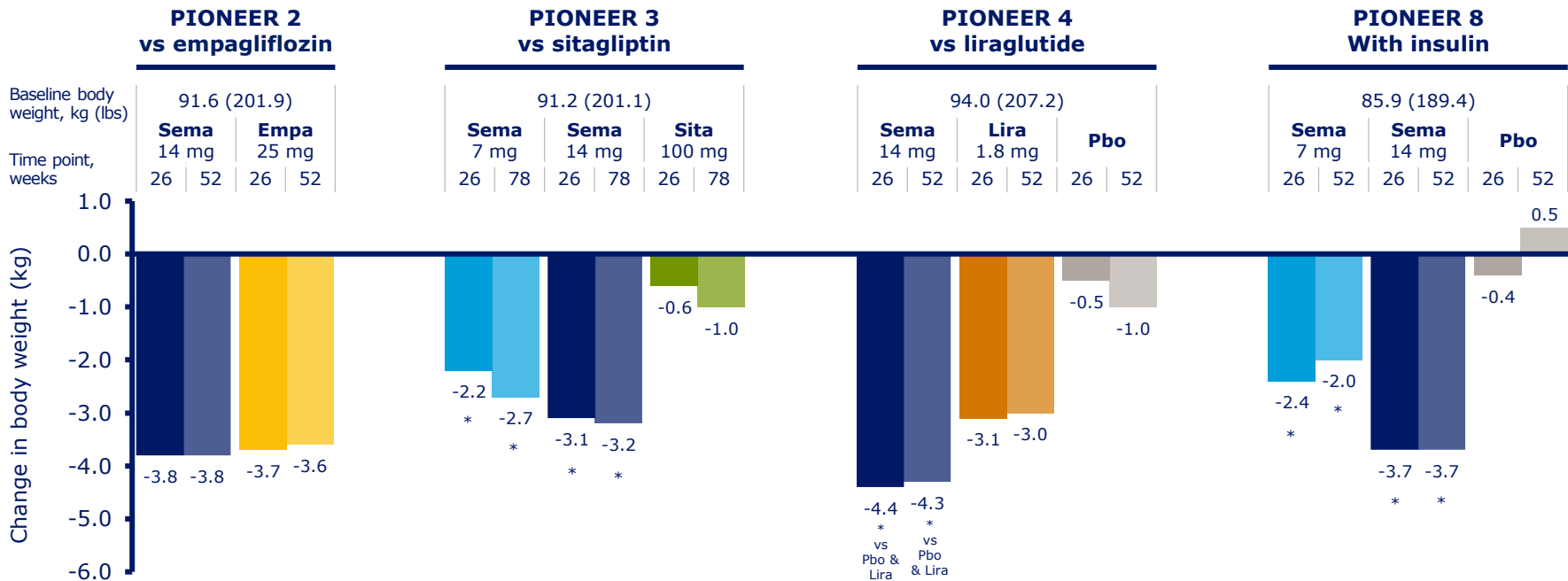
*Statistically significantly greater compared with placebo or active comparator.

Empa, empagliflozin; HbA_{1c}, glycated haemoglobin; Lira, liraglutide; Pbo, placebo; PIONEER, peptide innovation for early diabetes treatment; Sema, semaglutide; Sita, sitagliptin. Rodbard HW et al. *Diabetes Care* 2019;42(12):2272–2281; Rosenstock J et al. *JAMA* 2019;321:1466–80; Pratley R et al. *Lancet* 2019;394:39–50; Zinman B et al. *Diabetes Care* 2019;42(12):2262–2271.

Direct comparisons between trials should not be made due to differences in trial designs

PIONEER 2, 3, 4 and 8

CHANGE IN BODY WEIGHT OVER TIME – TREATMENT POLICY ESTIMAND



*Statistically significantly greater compared with placebo or active comparator. Empa, empagliflozin; Lira, liraglutide; Pbo, placebo; PIONEER, peptide innovation for early diabetes treatment; Sema, semaglutide; Sita, sitagliptin. Rodbard HW et al. *Diabetes Care* 2019;42(12):2272–2281; Rosenstock J et al. *JAMA* 2019;321:1466–80; Pratley R et al. *Lancet* 2019;394:39–50; Zinman B et al. *Diabetes Care* 2019;42(12):2262–2271.

Direct comparisons between trials should not be made due to differences in trial designs

PIONEER 2, 3, 4 and 8

CHANGE IN BODY WEIGHT OVER TIME – TRIAL PRODUCT ESTIMAND

