Supplemental Material

Long-term efficacy and safety of oral semaglutide, and the effect of switching from sitagliptin to oral semaglutide in patients with type 2 diabetes: a 52-week, randomized, open-label extension of the PIONEER 7 trial

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Estimands

According to International Council for Harmonisation (ICH) E9 (R1)*, an estimand description consists of the treatment condition of interest (e.g. the intervention of interest) plus four other components: 1) population, 2) endpoint, 3) intercurrent events and how they are accounted for, and 4) population level summary. In the table below, the attributes are described for the two estimands in the PIONEER program. Two intercurrent events were considered: trial product discontinuation and initiation of rescue medication.

The attributes of the two estimands according to ICH E9 (R1)*

Estimand	Population	Strategy for accounting for intercurrent events	Endpoints – switch part	Population level summary – switch part
Treatment policy	All randomized patients	Treatment policy strategy for both intercurrent events: • Trial product discontinuation • Initiation of rescue medication	Change from weeks 52 to 104 in: • HbA_{1c}† • Body weight (kg)† • Fasting plasma glucose • Body weight (%) • Body mass index • Waist circumference • Amylase • Lipase • Pulse rate • Systolic blood pressure • Diastolic blood pressure • Patient-reported outcomes (Diabetes Treatment Satisfaction Questionnaire, Short Form-36 version 2 (acute version))	Mean difference between treatments in change from weeks 52 to 104
			If a patient at week 104 achieves: • HbA_{1c} <7.0% • HbA_{1c} ≤6.5% • Weight loss ≥5% compared to week 52 • Composite endpoint: HbA_{1c} <7.0% without severe or blood glucose-confirmed symptomatic hypoglycemia and no weight gain	The odds ratio between treatments in reaching target
			Time to additional glucose-lowering medication after week 52	The hazard ratio between treatments
Trial product	All randomized patients	Hypothetical strategy for both intercurrent events: • Trial product discontinuation • Initiation of rescue medication	Change from baseline to week 104 in: • HbA_{1c} • Body weight (kg) • Fasting plasma glucose • Body weight (%) • Body mass index	Mean difference between treatments in change from weeks 52 to 104

Estimand	Population	Strategy for accounting for intercurrent events	Endpoints – switch part	Population level summary – switch part
			• Waist circumference • Amylase • Lipase • Pulse rate • Systolic blood pressure • Diastolic blood pressure • Patient-reported outcomes (Diabetes Treatment Satisfaction Questionnaire, Short Form-36 version 2 (acute version))	
			If a patient at week 104 achieves: • HbA_{1c} <7.0% • HbA_{1c} ≤6.5% • Weight loss ≥5% compared to week 52 • Composite endpoint: HbA_{1c} <7.0% without severe or blood glucose-confirmed symptomatic hypoglycemia and no weight gain	The odds ratio between treatments in reaching target
			Time to rescue medication	The hazard ratio between treatments

*International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9 (R1). Final version, adopted on November 20, 2019. Available at: https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf. (Accessed Jan 17, 2020).

†Confirmatory secondary endpoint at week 104.

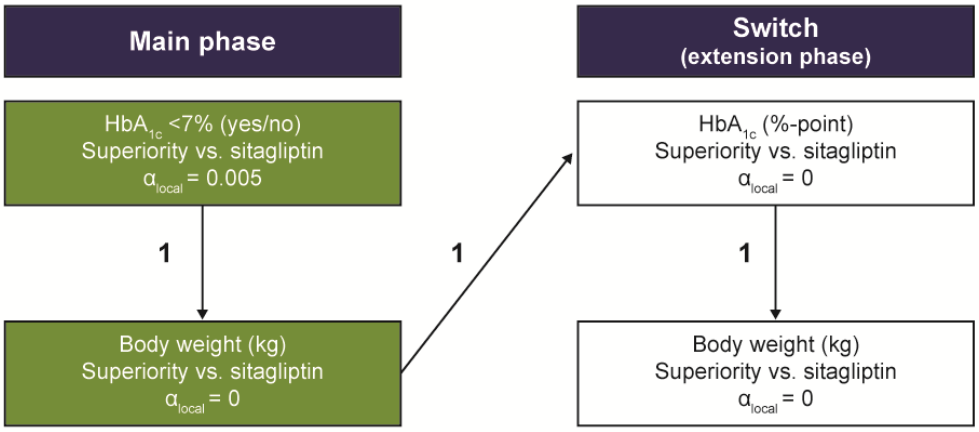
HbA_{1c}, glycated hemoglobin.

Statistical considerations

A hierarchical closed-testing strategy was used to preserve the overall type-1 error rate in the strong sense at a nominal two-sided 5% significance level for the treatment policy estimand only. The statistical testing strategy was based on the principle that glycemic effect was to be established in terms of HbA_{1c} superiority before testing for added benefits in terms of body weight superiority.

The first hypothesis to be tested was superiority on glycated hemoglobin (HbA_{1c}) of oral semaglutide versus sitagliptin in the main phase. The hypothesis was tested at the overall significance level (5%), while allocating a 0% local significance level to the remaining hypotheses. If the hypothesis was confirmed, the significance level was reallocated as indicated by the arrows in the figure below. Each hypothesis was tested at its updated local significance level (α-local) until all hypotheses had been confirmed or until no hypothesis could be confirmed.

As the two confirmatory hypotheses pertaining to the main phase of the trial were confirmed, the local significance level (α-local) was reallocated to the two confirmatory hypotheses in the switch part as specified in the figure below.



For the treatment policy estimand used in the switch part, the primary statistical analysis was based on a pattern mixture model using multiple imputation to impute missing data for week 104. It was assumed that the missing data mechanism was missing-at-random within the groups used for imputation. Missing data for week 104 were imputed within four groups of patients, depending on the treatment arm and treatment status. For this imputation approach, it was assumed that the distribution of missing data for patients in a specific treatment arm resembled the distribution of available data for other patients in the same treatment group and with the same treatment status at week 104.

Missing values for each group were imputed as follows:

- An analysis of covariance (ANCOVA) with region and stratification factors as categorical fixed effects and week 52 measurements as a covariate was fitted to observed values of the change from week 52 in HbA_{1c} or body weight at week 104.
- The estimated parameters for location and dispersion were used to impute 1000 values for each subject with missing week 104 data based on region and stratification factors as categorical fixed effects and week 52 measurements as a covariate. Thus, 1000 complete datasets were generated including observed and imputed values.

Subsequently, the analysis was done as follows:

- An ANCOVA model with treatment, region, and stratification factors as fixed effects and week 52 measurements as a covariate was fitted for each of the imputed datasets.
- The resulting 1000 estimates and variances were combined using Rubin's rule,[1] and the estimated treatment difference between oral semaglutide and sitagliptin together with two-sided 95% confidence interval and two-sided p value for testing no difference are presented.

For the trial product estimand used in the switch part for the confirmatory secondary endpoints, the primary analysis was based on a mixed model for repeated measurements (MMRM) that accounts for the uncertainty pertaining to missing data. The MMRM approach assumes that data are missing-at-random. As dependent variables, the MMRM model includes all post-week 52 values collected at scheduled visits up to and including week 104. The independent effects were treatment, region, and stratification factors as categorical fixed effects and the week 52 measurements as covariate, all nested within visit. An unstructured covariance matrix was employed for measurements within the same subject, assuming that measurements from different patients were independent. A restricted maximum likelihood approach was used.

For the switch part, the supportive continuous secondary efficacy endpoints were analyzed using similar statistical model approaches as for the confirmatory secondary endpoints, with the associated week 52 response as a covariate.

For the switch part, supportive binary secondary efficacy endpoints were analyzed using a logistic regression model with treatment, region, and stratification factors as fixed effects and the associated week 52 measurements as a covariate. To account for missing data, multiple imputation was used. As an exception, the binary endpoint 'HbA_{1c} <7.0% (53 mmol/mol) and no need for rescue medication after week 52' was only summarized descriptively.

For the switch part, the time to additional anti-diabetic medication/rescue medication endpoints were evaluated as specified below:

- Time to additional anti-diabetic medication (treatment policy estimand): time from rerandomization to initiation and/or intensification by a dose increase >20% of an additional anti-diabetic medication. Patients who had not initiated additional anti-diabetic medication were censored the day before the end-of-treatment visit (visit 19). The follow-up period was excluded, because some patients discontinued study drug at the end-of-treatment visit and might have needed additional glucose-lowering medication during the follow-up period. Patients who withdrew from the trial or were lost to follow-up were considered as having initiated an additional anti-diabetic medication.
- Time to rescue medication (trial product estimand): time from rerandomization to initiation and/or intensification of rescue medication. Patients who had not initiated rescue medication during the on-treatment period were censored one day before the last date on study drug.

The time-to-event endpoints were analyzed using a Cox proportional hazards model with treatment, region, and stratification factors as fixed effects and the week 52 HbA_{1c} measurements as a covariate.

The safety evaluation was primarily based on the on-treatment observation period, except for deaths and adverse event types with potentially long latency between onset and diagnosis, for which the in-trial observation period was used.

In-trial observation period:

- Durability part: starts at the date of randomization (visit 2) in the main phase; switch part: starts at the date of rerandomization (visit 10) in the extension phase.
- Includes the period after initiation of rescue medication and/or premature study drug discontinuation, if any.

On-treatment observation period:

- Durability: starts at the date of first dose of study drug in the main phase; switch: starts at the date of first dose of rerandomized study drug in the extension phase.
- Includes the period after initiation of rescue medication, if any.
- Excludes the period after premature study drug discontinuation, if any.

On-treatment without rescue medication observation period:

- Durability: starts at the date of first dose of study drug in the main phase; switch: starts at the date of first dose of rerandomized study drug in the extension phase.
- Excludes the period after initiation of rescue medication and/or premature study drug discontinuation, if any.

The trial sample size was calculated to ensure at least 90% power to confirm superiority of oral semaglutide versus sitagliptin for the primary endpoint (treatment policy estimand) of the main phase of the trial, with planned enrolment of 500 patients and random assignment to treatment to ensure this power was achieved. It was assumed that there would be an absolute difference in proportions of 15% and that the proportion of sitagliptin responders was distributed around 20–50%. Assumptions used in the sample size and power calculation for the main phase and extension phase (switch) are shown in the table below.

	Assumptions		**Power calculation**		
Endpoint	**Treatment effect**	**Standard deviation**	**Number of subjects**	**Marginal power**	**Conditional power**
Main phase					
HbA_{1c} <7.0% (yes/no)	15%-point difference		500	90%	90%
Change in body weight (kg)	2.5	4.0	500	>99%	90%
Extension phase (switch)					
Change in HbA_{1c} (%-point)	0.4	1.1	190	49%	44%
Change in body weight (kg)	2.5	4.0	190	91%	40%

1. Little RJA, Rubin DB. Statistical analysis with missing data. New York, NY: John Wiley & Sons 1987.

Online Supplemental Table 1 Additional glucose-lowering medication and rescue medication use

	Durability* (weeks 0 to 104)		**Switch† (weeks 52 to 104)**			
	Oral semaglutide (n=253)		**Oral semaglutide (n=100)**		**Sitagliptin (n=98)**	
	Additional glucose-lowering medication‡ n (%)	Rescue medication‡ n (%)	Additional glucose-lowering medication‡ n (%)	Rescue medication‡ n (%)	Additional glucose-lowering medication‡ n (%)	Rescue medication‡ n (%)
Any	46 (18.2)	25 (9.9)	15 (15.0)	9 (9.0)	26 (26.5)	23 (23.5)
Sulfonylureas	15 (5.9)	10 (4.0)	7 (7.0)	5 (5.0)	10 (10.2)	10 (10.2)
SGLT-2 inhibitors	12 (4.7)	8 (3.2)	3 (3.0)	2 (2.0)	10 (10.2)	10 (10.2)
DPP-4 inhibitors	10 (4.0)	0	4 (4.0)	0	0	0
Insulins	8 (3.2)	3 (1.2)	4 (4.0)	2 (2.0)	4 (4.1)	4 (4.1)
GLP-1 analogs	2 (0.8)	0	0	0	2 (2.0)	0
Other	2 (0.8)	2 (0.8)	0	0	0	0
Metformin	1 (0.4)	1 (0.4)	0	0	1 (1.0)	0
Alpha glucosidase inhibitors	1 (0.4)	1 (0.4)	0	0	0	0
Thiazolidinediones	1 (0.4)	1 (0.4)	1 (1.0)	0	7 (7.1)	7 (7.1)

*Includes all patients randomized to oral semaglutide at baseline (week 0).

†Includes all patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).

‡Additional glucose-lowering medication: defined as glucose-lowering medication (or a dose increase >20% of concomitant glucose-lowering medication) given to the subject after randomization (week 0) for the durability part or after rerandomization (week 52) for the switch part, and before the planned end-of-treatment visit. Rescue medication: a subset of additional glucose-lowering medication and defined as glucose-lowering medication given as add-on to study drug (i.e. before the last day on study drug).

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose co-transporter 2.

Online Supplemental Table 2 Supportive secondary endpoints not reported in the main text for the durability part (weeks 0 to 104)

	Oral semaglutide (n=253)	
	In-trial observation period	**On-treatment without rescue observation period**
Fasting plasma glucose, mmol/L		
*Week 52**		
n	182	175
Observed mean change from baseline (SD)	–2.59 (2.15)	–2.51 (2.12)
Week 104		
n	178	148
Observed mean change from baseline (SD)	–2.19 (2.84)	–2.12 (2.32)
Body weight, %		
*Week 52**		
n	185	178
Observed mean change from baseline (SD)	–3.06 (4.26)	–3.11 (4.29)
Week 104		
n	180	154
Observed mean change from baseline (SD)	–4.03 (5.75)	–4.36 (5.98)
BMI, kg/m^2		
*Week 52**		
n	185	178
Observed mean change from baseline (SD)	–1.0 (1.4)	–1.0 (1.4)
Week 104		
n	180	154
Observed mean change from baseline (SD)	–1.3 (1.9)	–1.4 (2.0)
Waist circumference, cm		
*Week 52**		
n	183	176
Observed mean change from baseline (SD)	–2.5 (5.3)	–2.4 (5.4)
Week 104		
n	178	152
Observed mean change from baseline (SD)	–2.5 (6.3)	–3.0 (6.3)
HbA_{1c} <7.0% (<53 mmol/mol)		
*Week 52**		

	Oral semaglutide (n=253)	
	In-trial observation period	**On-treatment without rescue observation period**
n	183	177
Observed proportion achieving outcome, n (%)	115 (62.8)	114 (64.4)
Week 104		
n	180	150
Observed proportion achieving outcome, n (%)	101 (56.1)	91 (60.7)
HbA_{1c} ≤6.5% (<48 mmol/mol)		
*Week 52**		
n	183	177
Observed proportion achieving outcome, n (%)	65 (35.5)	64 (36.2)
Week 104		
n	180	150
Observed proportion achieving outcome, n (%)	63 (35.0)	59 (39.3)
Body weight loss ≥5%		
*Week 52**		
n	185	178
Observed proportion achieving outcome, n (%)	49 (26.5)	48 (27.0)
Week 104		
n	180	154
Observed proportion achieving outcome, n (%)	64 (33.9)	58 (37.7)
HbA_{1c} <7.0% (<53 mmol/mol) without severe or BG-confirmed symptomatic hypoglycemic episodes† and without body weight gain		
*Week 52**		
n	183	177
Observed proportion achieving outcome, n (%)	90 (49.2)	89 (50.3)
Week 104		
n	180	150
Observed proportion achieving outcome, n (%)	73 (40.6)	67 (44.7)
HbA_{1c} <7.0% (<53 mmol/mol) or HbA_{1c} reduction ≥1% point (<10.9 mmol/mol)		
*Week 52**		
n	183	177
Observed proportion achieving outcome, n (%)	155 (84.7)	154 (87.0)

	Oral semaglutide (n=253)	
	In-trial observation period	**On-treatment without rescue observation period**
Week 104		
n	180	150
Observed proportion achieving outcome, n (%)	126 (70.0)	113 (75.3)

*Among patients continuing from the main phase into the extension phase.

†An episode that is severe according to the American Diabetes Association classification or BG-confirmed by a plasma glucose value <3.1 mmol/L (<56 mg/dL) with symptoms consistent with hypoglycemia.

BG, blood glucose; BMI, body mass index; HbA_{1c}, glycated hemoglobin; n, number of patients with non-missing information; SD, standard deviation.

Online Supplemental Table 3 On-treatment adverse events by system organ class*

Patients with events, n (%)	Durability† (weeks 0 to 104)	Switch‡ (weeks 52 to 104)	
	Oral semaglutide (n=253)	Oral semaglutide (n=100)	Sitagliptin (n=97)§
Any event	215 (85.0)	75 (75.0)	67 (69.1)
Gastrointestinal disorders	126 (49.8)	41 (41.0)	14 (14.4)
Infections and infestations	99 (39.1)	27 (27.0)	26 (26.8)
Musculoskeletal and connective tissue	61 (24.1)	14 (14.0)	19 (19.6)
Nervous system disorders	57 (22.5)	14 (14.0)	13 (13.4)
Metabolism and nutrition disorders	50 (19.8)	10 (10.0)	8 (8.2)
Investigations	38 (15.0)	7 (7.0)	8 (8.2)
General disorders and administration	35 (13.8)	6 (6.0)	4 (4.1)
Eye disorders	28 (11.1)	13 (13.0)	12 (12.4)
Injury, poisoning, and procedural complications	26 (10.3)	6 (6.0)	7 (7.2)
Skin and subcutaneous tissue disorders	23 (9.1)	7 (7.0)	10 (10.3)
Renal and urinary disorders	22 (8.7)	2 (2.0)	2 (2.1)
Cardiac disorders	17 (6.7)	4 (4.0)	6 (6.2)
Respiratory, thoracic, and mediastinal disorders	17 (6.7)	5 (5.0)	13 (13.4)
Vascular disorders	17 (6.7)	5 (5.0)	6 (6.2)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	15 (5.9)	2 (2.0)	2 (2.1)
Reproductive system and breast disorders	12 (4.7)	2 (2.0)	1 (1.0)
Psychiatric disorders	10 (4.0)	2 (2.0)	2 (2.1)
Hepatobiliary disorders	8 (3.2)	2 (2.0)	2 (2.1)
Ear and labyrinth disorders	7 (2.8)	3 (3.0)	1 (1.0)
Blood and lymphatic system disorders	6 (2.4)	2 (2.0)	4 (4.1)
Endocrine disorders	6 (2.4)	3 (3.0)	2 (2.1)
Immune system disorders	4 (1.6)	0	1 (1.0)
Surgical and medical procedures	4 (1.6)	1 (1.0)	2 (2.1)
Congenital, familial, and genetic disorders	3 (1.2)	0	0

Social circumstances	1 (0.4)	0	1 (1.0)

*MedDRA version 20.1.

†Patients randomized to oral semaglutide at baseline (week 0).

‡Patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).

§One patient was rerandomized to sitagliptin, but was not exposed to the study drug and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).

MedDRA, Medical Dictionary for Regulatory Activities.

Online Supplemental Table 4 On-treatment adverse events leading to premature trial product discontinuation

	Durability* (weeks 0 to 104)		**Switch† (weeks 52 to 104)**			
	Oral semaglutide (n=253)		**Oral semaglutide (n=100)**		**Sitagliptin (n=97)‡**	
	Patients with at least one event n (%)	Episodes, n	Patients with at least one event n (%)	Episodes, n	Patients with at least one event n (%)	Episodes, n
Gastrointestinal disorders	15 (5.9)	20	4 (4)	7	0	0
Nausea	7 (2.8)	7	2 (2)	2	0	0
Diarrhea	3 (1.2)	3	1 (1)	1	0	0
Abdominal pain	2 (0.8)	2	0	0	0	0
Abdominal pain upper	2 (0.8)	2	2 (2)	2	0	0
Dyspepsia	2 (0.8)	2	0	0	0	0
Vomiting	2 (0.8)	2	1 (1)	1	0	0
Abdominal discomfort	1 (0.4)	1	0	0	0	0
Crohn’s disease	1 (0.4)	1	0	0	0	0
Constipation	0	0	1 (1)	1	0	0
Neoplasms benign, malignant and unspecified	5 (2.0)	5	0	0	0	0
Adenocarcinoma of colon	2 (0.8)	2	0	0	0	0
Choroid melanoma	1 (0.4)	1	0	0	0	0
Hepatocellular carcinoma	1 (0.4)	1	0	0	0	0
Prostate cancer	1 (0.4)	1	0	0	0	0
Lung cancer metastatic	0	0	1 (1)	1	0	0

Other system organ class	10 (4.0)	11	2 (2)	2	0	0
Pancreatic enzymes increased	1 (0.4)	1	0	0	0	0
Weight decreased	1 (0.4)	1	0	0	0	0
Decreased appetite	2 (0.8)	2	0	0	0	0
Dysgeusia	2 (0.8)	2	0	0	0	0
Dizziness	1 (0.4)	1	0	0	0	0
Tachycardia	1 (0.4)	1	0	0	0	0
Fatigue	1 (0.4)	2	0	0	0	0
Pruritis	1 (0.4)	1	0	0	0	0
Eyelid edema	0	0	1 (1)	1	0	0
Urticaria	0	0	1 (1)	1	0	0

*Includes all patients randomized to oral semaglutide at baseline (week 0).

†Includes all patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).

‡One patient was rerandomized to sitagliptin, but was not exposed to the study drug and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).

Online Supplemental Table 5 On-treatment hypoglycemic episodes

	Durability* (weeks 0 to 104)		**Switch† (weeks 52 to 104)**			
	Oral semaglutide (n=253)		**Oral semaglutide (n=100)**		**Sitagliptin (n=97)‡**	
	Patients with at least one event n (%)	Episodes, n	Patients with at least one event n (%)	Episodes, n	Patients with at least one event n (%)	Episodes, n
Severe hypoglycemic episodes§	0	0	0	0	0	0
Severe or BG-confirmed symptomatic hypoglycemic episodes¶	18 (7.1)	45	2 (2.0)	2	4 (4.1)	12
Nocturnal	4 (1.6)	8	0	0	0	0
Episodes in patients on SU	17 (13.7)** (n=124)	44	1 (2.0)** (n=51)	1	2 (4.3)** (n=47)	10
Episodes in patients not on SU	1 (0.8)** (n=129)	1	1 (2.0)** (n=49)	1	2 (4.0)** (n=50)	2
Hypoglycemic episodes by ADA classification††	58 (22.9)	328	9 (9.0)	43	13 (13.4)	52
Episodes in patients on SU	46 (37.1)** (n=124)	311	6 (11.8)** (n=51)	39	7 (14.9)** (n=47)	43
Episodes in patients not on SU	12 (9.3)** (n=129)	17	3 (6.1)** (n=49)	4	6 (12.0)** (n=50)	9

*Includes all patients randomized to oral semaglutide at baseline (week 0).

†Includes all patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).

‡One patient was rerandomized to sitagliptin, but was not exposed to the study drug and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).

§An episode that is severe according to ADA classification (requiring assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions).[1]

¶An episode that is severe according to ADA classification§ or BG-confirmed by a plasma glucose value <3.1 mmol/L (<56 mg/dL) with symptoms consistent with hypoglycemia.

**Percentages relative to the total number of patients (n) within the relevant SU treatment status group.

††An episode of hypoglycemia that meets ADA classification for hypoglycemia, including episodes classified as severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, pseudo-hypoglycemia, and unclassifiable (n=1, four episodes)[1]

ADA, American Diabetes Association; BG, blood glucose; SU, sulfonylurea.

1. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013;36(5):1384–95.

Online Supplemental Table 6 EAC-confirmed events, excluding malignant neoplasms

	Durability* (weeks 0 to 104)		**Switch† (weeks 52 to 104)**			
	Oral semaglutide (n=253)		**Oral semaglutide (n=100)**		**Sitagliptin (n=97)‡**	
	Patients with at least one event n (%)	Events, n	Patients with at least one event n (%)	Events, n	Patients with at least one event n (%)	Events, n
Deaths						
In-trial	0	0	0	0	0	0
Acute kidney injury						
On-treatment	2 (0.8)	2	0	0	0	0
Acute pancreatitis						
On-treatment	0	0	0	0	0	0
Cardiovascular events						
In-trial	1 (0.4)	1	0	0	1 (1.0)	1
Acute coronary syndrome	1 (0.4)	1	0	0	0	0
Acute myocardial infarction	1 (0.4)	1	0	0	0	0
Cerebrovascular events	0	0	0	0	0	0
Heart failure requiring hospitalization	0	0	0	0	1 (1.0)	1
Lactic acidosis						
On-treatment	0	0	0	0	0	0

	Durability* (weeks 0 to 104)		**Switch† (weeks 52 to 104)**			
	Oral semaglutide (n=253)		**Oral semaglutide (n=100)**		**Sitagliptin (n=97)‡**	
	Patients with at least one event n (%)	Events, n	Patients with at least one event n (%)	Events, n	Patients with at least one event n (%)	Events, n
Thyroid-related events						
In-trial	0	0	0	0	0	0

*Patients randomized to oral semaglutide at baseline (week 0).

†Patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).

‡One patient was rerandomized to sitagliptin but was not exposed to the study drug, and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).

EAC, event adjudication committee.

Online Supplemental Table 7 EAC-confirmed malignant neoplasms

	Durability* (weeks 0 to 104)				**Switch† (weeks 52 to 104)**							
	Oral semaglutide (n=253)				**Oral semaglutide (n=100)**				**Sitagliptin (n=97)‡**			
	Patients with at least one event n (%)	Events, n	Events per 100 PY	Time of onset (day)§	Patients with at least one event n (%)	Events, n	Events per 100 PY	Time of onset (day)§	Patients with at least one event n (%)	Events, n	Events per 100 PY	Time of onset (day)§
Malignant neoplasm¶												
In-trial	11 (4.3)	12	2.6		2 (2.0)	2	1.8		0	0	0	
Breast cancer	2 (0.8)	2	0.4	315 367	0	0	0	-	0	0	0	-
Colorectal cancer	2 (0.8)	2	0.4	297 221	0	0	0	-	0	0	0	-
Gastrointestinal cancer	2 (0.8)	2	0.4		0	0	0		0	0	0	
Liver	1 (0.4)	1	0.2	249	0	0	0	-	0	0	0	-
Stomach	1 (0.4)	1	0.2	330	0	0	0	-	0	0	0	-
Genitourinary cancer	0	0	0		1 (1.0)	1	0.9		0	0	0	
Kidney	0	0	0	-	1 (1.0)	1	0.9	132	0	0	0	-
Gynecologic cancer	1 (0.4)	2	0.4		0	0	0		0	0	0	
Ovary	1 (0.4)	1	0.2	697	0	0	0	-	0	0	0	-
Uterus	1 (0.4)	1	0.2	697	0	0	0	-	0	0	0	-

	Durability* (weeks 0 to 104)				Switch† (weeks 52 to 104)							
	Oral semaglutide (n=253)				Oral semaglutide (n=100)				Sitagliptin (n=97)‡			
	Patients with at least one event n (%)	Events, n	Events per 100 PY	Time of onset (day)§	Patients with at least one event n (%)	Events, n	Events per 100 PY	Time of onset (day)§	Patients with at least one event n (%)	Events, n	Events per 100 PY	Time of onset (day)§
Lung and pleura cancer	0	0	0		1 (1.0)	1	0.9		0	0	0	
Lung cancer	0	0	0	-	1 (1.0)	1	0.9	258	0	0	0	-
Skin cancer	2 (0.8)	2	0.4		0	0	0		0	0	0	
Malignant melanoma	1 (0.4)	1	0.2	594	0	0	0	-	0	0	0	-
Skin cancer other than melanoma	1 (0.4)	1	0.2	254	0	0	0	-	0	0	0	-
Other primary site	1 (0.4)	1	0.2	11	0	0	0	-	0	0	0	-
Prostate cancer	1 (0.4)	1	0.2	315	0	0	0	-	0	0	0	-

*Patients randomized to oral semaglutide at baseline (week 0).

†Patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).

‡One patient was rerandomized to sitagliptin, but was not exposed to the study drug and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).

§Time of onset: for the durability part, trial day of onset of event according to EAC. For switch part, trial day relative to rerandomization (week 52) of onset of event according to EAC.

¶One event of malignant anorectal neoplasm in the durability part was reported after database lock; this event had onset during the trial, but was not sent for adjudication due to being reported after database lock.

EAC, event adjudication committee; PY, patient years.

Online Supplemental Table 8 In-trial diabetic retinopathy and related complications

	Durability* (weeks 0 to 104)		**Switch† (weeks 52 to 104)**			
	Oral semaglutide (n=253)		**Oral semaglutide (n=100)**		**Sitagliptin (n=97)‡**	
	Patients with at least one event n (%)	Events, n	Patients with at least one event n (%)	Events, n	Patients with at least one event n (%)	Events, n
Events	13 (5.1)	16	4 (4.0)	4	2 (2.1)	2
Preferred terms§						
Diabetic retinopathy	10 (4.0)	11	3 (3.0)	3	1 (1.0)	1
Retinal hemorrhage	2 (0.8)	2	0	0	1 (1.0)	1
Macular edema	1 (0.4)	1	0	0	0	0
Retinopathy	1 (0.4)	1	0	0	0	0
Vitreous detachment	1 (0.4)	1	1 (1.0)	1	0	0

*Patients randomized to oral semaglutide at baseline (week 0).

†Patients previously randomized to sitagliptin at baseline (week 0) and rerandomized to either oral semaglutide or sitagliptin at the start of the extension phase (week 52).

‡One patient was rerandomized to sitagliptin, but was not exposed to the study drug and was therefore included in the full analysis set for the sitagliptin group (n=98) and excluded from the safety analysis set (n=97).

§MedDRA version 20.1.

MedDRA, Medical Dictionary for Regulatory Activities.

Online Supplemental Table 9 Other safety assessments in the durability part (weeks 0 to 104)

	Oral semaglutide (n=253)	
	In-trial observation period	**On-treatment observation period**
Systolic blood pressure, mm Hg		
*Week 52**		
n	185	185
Observed mean (SD) change from baseline	–4 (14)	–4 (14)
Week 104		
n	180	176
Observed mean (SD) change from baseline	–3 (14)	–3 (14)
Diastolic blood pressure, mm Hg		
*Week 52**		
n	185	185
Observed mean (SD) change from baseline	–1 (9)	–1 (9)
Week 104		
n	180	176
Observed mean (SD) change from baseline	–1 (9)	–1 (9)
Pulse rate, beats/min		
*Week 52**		
n	185	185
Observed mean (SD) change from baseline	2 (9)	2 (9)
Week 104		
n	180	176
Observed mean (SD) change from baseline	2 (9)	2 (9)
eGFR, mL/min/1.73 m^2		
*Week 52**		
n	184	184
Geometric mean (CV) ratio to baseline	0.99 (7.8)	0.99 (7.8)
Week 104		

	Oral semaglutide (n=253)	
	In-trial observation period	**On-treatment observation period**
n	179	170
Geometric mean (CV) ratio to baseline	0.96 (10.4)	0.97 (9.5)

*Among patients continuing from the main phase into the extension phase.

CV, coefficient of variation; eGFR, estimated glomerular filtration rate; n, number of patients contributing to the summary statistics.

Online Supplemental Table 10 Supportive endpoints at week 104 not reported in the main text for switch part

	Treatment policy estimand		Trial product estimand	
	Oral semaglutide (n=100)	**Sitagliptin (n=98)**	**Oral semaglutide (n=100)**	**Sitagliptin (n=98)**
Body weight, %				
n	100	98	100	98
Estimated mean change from baseline	–2.9	–0.7	–3.3	–0.8
ETD (95% CI)	–2.1 (–3.5 to –0.7)		–2.5 (–4.1 to –1.0)	
P value	0.0036		0.0015	
BMI, kg/m^2				
n	100	98	100	98
Estimated mean change from baseline	–0.8	–0.4	–1.0	–0.4
ETD (95% CI)	–0.4 (–0.9 to 0.1)		–0.6 (–1.1 to 0.0)	
P value	0.1032		0.0543	
Waist circumference, cm				
n	100	98	100	98
Estimated mean change from baseline	–1.5	–0.9	–2.1	–0.8
ETD (95% CI)	–0.6 (–2.0 to 0.9)		–1.3 (–3.0 to 0.3)	
P value	0.4386		0.1042	

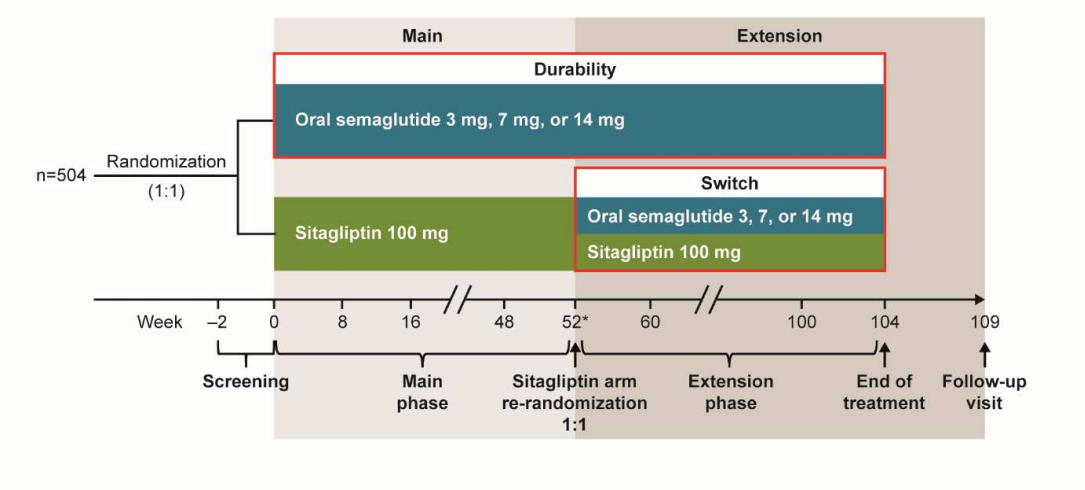
BMI, body mass index; ETD, estimated treatment difference; n, number of patients contributing to the analysis.

Online Supplemental Table 11 Other safety assessments in the switch part (on-treatment)

	Switch (weeks 52 to 104)	
	Oral semaglutide (n=100)	**Sitagliptin (n=97)**
Systolic blood pressure, mm Hg		
n	100	97
Estimated mean change from baseline at week 104	–3	2
ETD (95% CI)	–5 (–9 to –1)	
P value	0.0204	
Diastolic blood pressure, mm Hg		
n	100	97
Estimated mean change from baseline at week 104	–1	–0
ETD (95% CI)	–1 (–4 to 2)	
P value	0.4213	
Pulse rate, beats/min		
n	100	97
Estimated mean change from baseline at week 104	1	–0
ETD (95% CI)	2 (–1 to 4)	
P value	0.1787	
eGFR, mL/min/1.73 m^2		
n	84	92
Geometric mean (CV) ratio to baseline at week 104	0.97 (9.0)	0.97 (10.2)

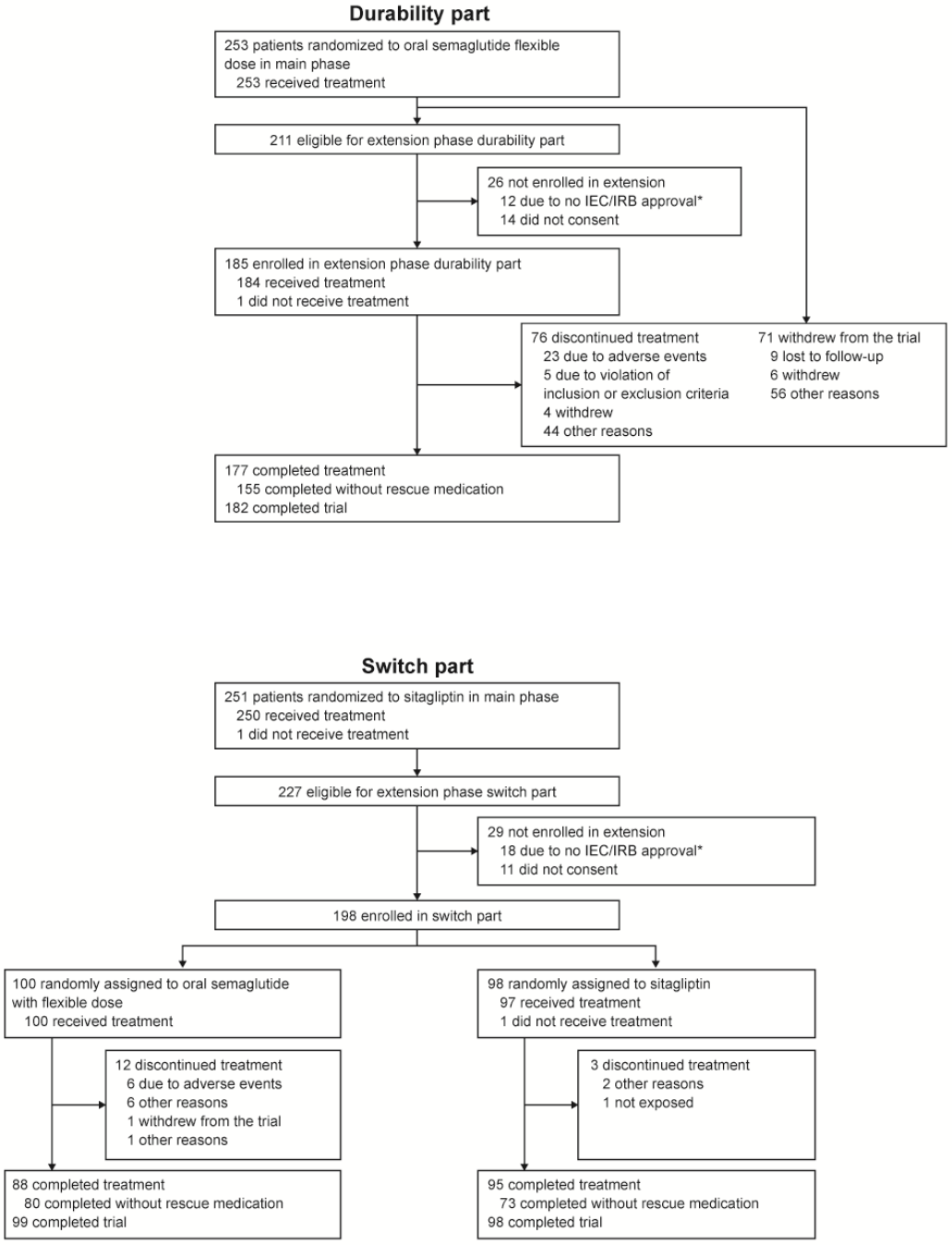
CV, coefficient of variation; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; n, number of patients contributing to the analysis.

Online Supplemental Figure 1 Trial design



*After 52 weeks, patients could either undergo a 5-week follow-up period and complete the trial or, after consenting, they could continue in the 52-week extension phase. The extension phase is marked in grey; the durability part (main + extension phase) and the switch part (extension phase only) are marked in red.

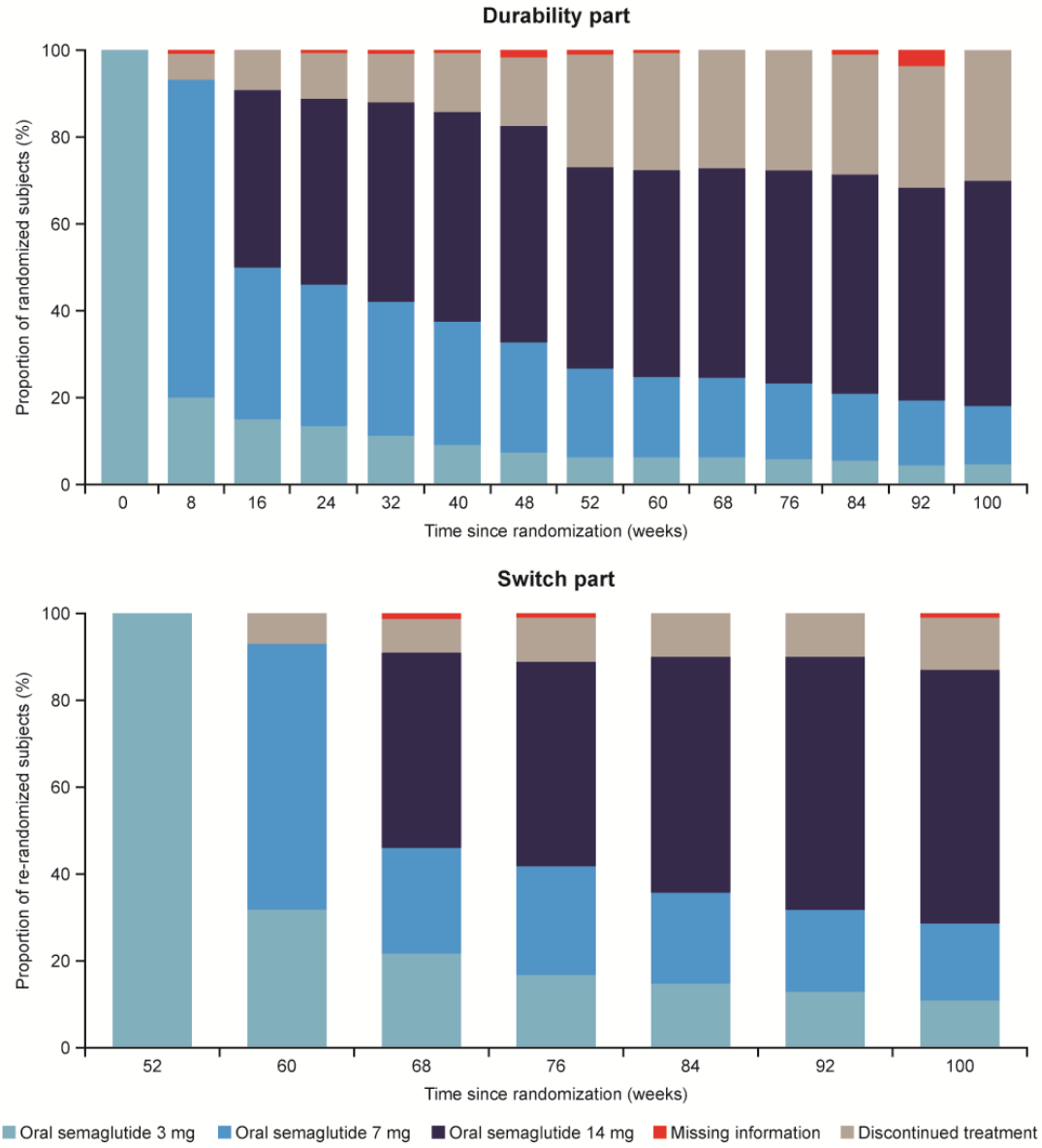
Online Supplemental Figure 2 Patient disposition



*IEC/IRB approval was not secured in time for the start of the extension phase for the two study sites in Brazil.

IEC, Independent Ethics Committee; IRB, Institutional Review Board.

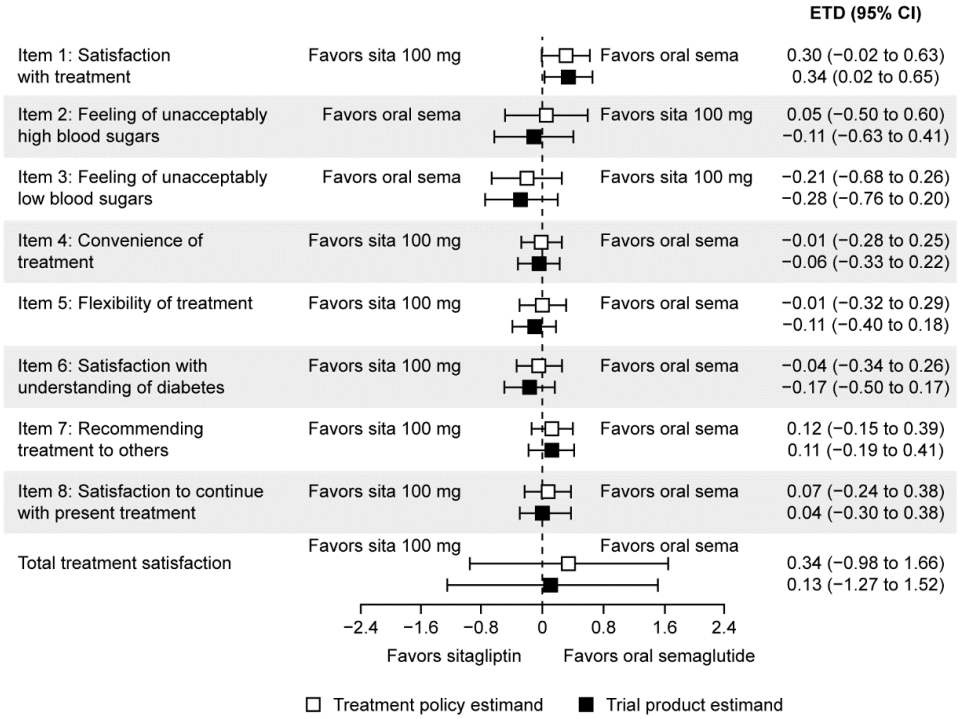
Online Supplemental Figure 3 Oral semaglutide dose by week in the durability and switch parts. Dose levels correspond to the prescribed dose at a given week



In the durability part, among the 184 patients continuing into the extension phase who were exposed to study drug at week 52, 16 were receiving oral semaglutide 3 mg, 51 were receiving oral semaglutide 7 mg, and 117 were receiving oral semaglutide 14 mg; among the 177 patients still receiving treatment at the week 100 time point, 10, 37, and 123 patients were receiving oral semaglutide 3, 7, and 14 mg, respectively.

In the switch part, of the 100 patients rerandomized to oral semaglutide at week 52, 88 patients remained on-treatment at week 100, with 13, 19, and 56 patients receiving oral semaglutide 3, 7, and 14 mg, respectively.

Online Supplemental Figure 4 Change from week 52 in Diabetes Treatment Satisfaction Questionnaire scores at week 104 in the switch part



ETD, estimated treatment difference; flex, flexible dosing; sema, semaglutide; sita, sitagliptin.

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*Approved sites for main phase but not extension phase of trial.