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Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized Clinical Trial Comparing the Efficacy and Safety of Oral Semaglutide Monotherapy with Placebo in Patients with Type 2 Diabetes. Diabetes Care. [submitted]

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Supplementary Appendix 1. PIONEER 1 investigators.

Algeria: Krim Belkacem, MDD El Harrach, Algiers; Nabil Chiali, UH of Douera, Algiers; Samia Bourezane, Bouz DH Algiers, Algiers; Rachida Guermaz, CHU-BIRTRARIA, Algiers.

Bulgaria: Plamen Popivanov, UMHAT Aleksandrovska, Sofia; Ivaylo Lefterov, Fifth MHAT-Sofia, Sofia; Tsvetalina Tankova, USHATE Acad. Ivan Penchev, Sofia.

Czech Republic: Martina Koskova, NMLB, Mlada Boleslav; Miroslava Hudcova, DIAMIN s.r.o., Chrudim; Alica Vesela, Edumed Broumov, Broumov; Anna Rancova, Diabetologie, Olomouc; Martin Haluzik, Endokrinologicky ustav; Prague 1.

Japan: Arihiro Kiyosue, Tokyo-Eki Center-building Clin, Chuo-ku, Tokyo; Osamu Matsuoka, ToCROM Clinic, Shinjuku-ku, Tokyo; Satoshi Inoue, OCROM Clinic, Internal Medicine, Suita-shi, Osaka; Yasuo Terauchi, Yokohama City Univ. HP, Yokohama, Kanagawa; Yasushi Fukushima, Fukuwa Clinic, Chou-ko Tokyo; Yumiko Ide, Tokyo Center Clinic, Tokyo.

Mexico: Rafael Margarito Violante Ortiz, CEI, Tampico; Enrique Morales Villegas, Centro de Investigación Cardiometabólica, Aguascalientes.

Russian Federation: Albina Golovach, Clinic NTM, Dzerzhinskiy; Diana Alpenidze, City Out-pt Depart. #117, SPb, Saint-Petersburg; Elena Frolova, Polyclinic #2 in Yoshkar-Ola, Yoshkar-Ola; Elena Zhdanova, VRCCDC, Voronezh; Lidia Belousova, Med Alians LLC, Saint-Petersburg; Ludmila Ruyatkina, LLC 'Healthy Family', Novosibirsk; Olga Ershova, Emergency Hospital, Yaroslavl; Yulia Samoilova, SSMU, Tomsk; Svetlana Zyangirova, Kazan Endocrinology Dispensary, Kazan.

Serbia: Katarina Lalic, Clinic for Endocrinology, Diabetes and Metabolic Disorders, Belgrade; Nebojsa Lalic, Clinic for Endocrinology, Diabetes and Metabolic Disorders, Belgrade; Teodora Beljic Zivkovic, CHC Zvezdara, Belgrade.

Turkey: Esra Ataoglu, Haseki Hastanesi, Istanbul; Okan Bakiner, Baskent Universitesi Adana, Adana; Akin Dayan, Haydarpasa Numune, Istanbul; Mehmet Sargin, Goztepe Hospital, Istanbul; Meral Mert, Bakirkoy EAH, Istanbul; Mine Adas, Okmeydani Egitim, Istanbul; Omur Tabak, Kanuni EAH, Istanbul; Yuksel Altuntas, Sisli Etfal Hospital, Istanbul.

United States of America: Alexander Murray, PharmQuest, Greensboro, North Carolina; Ali Iranmanesh, Salem VA Medical Center, Salem, Virginia; Aron Schlau, Palm Harbor Medical Center, Palm Harbor, Florida; Bram Wieskopf, North Georgia Clinical Research, Woodstock, Georgia; Brian Snyder, Southgate Medical Group LLP, West Seneca, New York; Carl Griffin, Lynn Health Science Institute, Oklahoma City, Oklahoma; Charles Fogarty, Spartanburg Medical Research, Spartanburg, South Carolina; Charles Lovell, York Clinical Research LLC, Norfolk, Virginia; Dale Allison, Hillcrest Family Center, Waco, Texas; David Fitz-Patrick, East West Med Research Institute, Honolulu, Hawaii; David Grant, Sun Research Institute, San Antonio, Texas; David Klonoff, Mills-Peninsula Health Service, San Mateo, California; Dwayne Williams, Sugar Land, Texas; Eddie Armas, Well Pharma Medical Research, Miami, Florida; Eileen Palace, The Center for Sexual Health, Metairie, Louisiana; Gary Ruoff, Westside Family Medical Center, Michigan; Gilbert Martinez, Catalina Research Institute LLC, Montclair, California; Gilberto Perez, Reliable Clinical Research, Hialeah, Florida; Harold Bays, L-MARC Research Center, Louisville, Kentucky; Horia Tatu, Remedica LLC, Rochester, Michigan; James Maynard, CTI Clinical Research Center, Cincinnati, Ohio; Jeanne-Elyse Cedeno, Family Clinical

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Trials, Pembroke Pines, Florida; Vanita Aroda, Jean Park, MedStar Health Research Institute, Hyattsville, Maryland; Jennefer Sutton, Victorium Clinical Research, San Antonio, Texas; Joe Pouzar, Centex Studies Inc., Houston, Texas; John Bertsch, Ohio Clinical Research LLC, Willoughby Hills, Ohio; Jonathan Condit, American Health Network of IN, Muncie, Indiana; Jorge Serje, NY Total Medical Care PC, Brooklyn, New York; Josel Cabaccan, San Jose, California; Joseph Risser, San Diego Family Care, San Diego, California; Juan Frias, National Research Institute, Los Angeles, California; Julio Rosenstock, Dallas Diabetes Research Center, Dallas, Texas; Kanagaratnam Sivalingam, First Valley Medical Group, Lancaster, California; Kelli Maw, Meridien Research, Spring Hill, Florida; Lenita Hanson, Hanson Clinical Research Center, Port Charlotte, Florida; Liana Billings, NorthShore University, Skokie, Illinois; Lisa Connery, Intend Research, Norman, Oklahoma; Mario Juarez, Panacea Clinical Research, San Antonio, Texas; Michael Lillestol, Lillestol Research LLC, Fargo, North Dakota; Neil Fraser, Arcturus Healthcare PLC, Troy, Michigan; Paul Beckett, Elite Clinical Trials, Blackfoot, Idaho; Ralph Wade, Wade Family Medicine, Bountiful, Utah; Raul Gaona, Briggs Clinical Research LLC, San Antonio, Texas; Richard Jackson, Dominion Medical Associates, Richmond, Virginia; Robert DeLuca, Care Research Inc., Doral, Florida; Sady Alpizar, Clinical Research Trials of Florida, Tampa, Florida; Sharon Herring, CORE, Philadelphia, Pennsylvania; Stanley Stringam, Saltzer Medical Group Research, Nampa, Idaho; Steven Bauer, OnSite Clinical Solutions LLC, Charlotte, North Carolina; Sumana Gangi, Southern Endocrinology Association, Mesquite, Texas; Teresa Sligh, Providence Clinical Research, North Hollywood, California; Wentworth Jarrett, Alpha Science Research LLC, Miami, Florida; William Fitzgibbons, Clinical Research Advantage, Elkhorn, Nebraska.

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Supplementary Appendix 2. Estimands.

According to draft ICH E9 (R1) an estimand description consists of four components: 1) population, 2) endpoint, 3) intercurrent events and how they are accounted for and 4) population level summary. In the table below, the four attributes are described for the two estimands in PIONEER 1. Two intercurrent events were considered: trial product discontinuation and initiation of rescue medication.

The attributes of the two estimands according to draft ICH E9 (R1)[1]

Estimand	**Population**	**Strategy for accounting for intercurrent events**	**Endpoints**	**Population level summary**
Treatment policy estimand	All randomized patients	Treatment policy: • Trial product discontinuation • Initiation of rescue medication	Change from baseline to week 26 in • HbA_{1c}* • Body weight (kg) * • Fasting plasma glucose • SMBG • BMI • Pulse • Systolic blood pressure • Diastolic blood pressure	Mean difference between treatments in change from baseline to week 26
			Change from baseline to week 26 in • Fasting pro-insulin • Fasting glucagon • Fasting C peptide • Fasting insulin • C-reactive protein • HOMA-B • HOMA-IR • Total cholesterol • Low-density lipoprotein cholesterol • High-density lipoprotein cholesterol • Triglycerides	The geometric mean ratio between treatments
			If a patient at week 26 achieves: • HbA_{1c} <7.0% • HbA_{1c} ≤6.5% • Body weight loss ≥5% • Body weight loss ≥10% • Composite: HbA_{1c} <7% without hypoglycemia and no weight gain • Composite: HbA_{1c} reduction ≥1% and body weight loss ≥3%	The odds ratio between treatments in reaching target

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Estimand	**Population**	**Strategy for accounting for intercurrent events**	**Endpoints**	**Population level summary**
Trial product estimand	All randomized patients	Hypothetical strategy: • Trial product discontinuation • Initiation of rescue medication	Change from baseline to week 26 in • HbA_{1c} • Body weight (kg) • Fasting plasma glucose • SMBG • BMI • Pulse • Systolic blood pressure • Diastolic blood pressure	Mean difference between treatments in change from baseline to week 26
			Change from baseline to week 26 in • Fasting pro-insulin • Fasting glucagon • Fasting C peptide • Fasting insulin • C-reactive protein • HOMA-B • HOMA-IR • Total cholesterol • Low-density lipoprotein cholesterol • High-density lipoprotein cholesterol • Triglycerides	
			If a patient at week 26 achieves: • HbA_{1c} <7.0% • HbA_{1c} ≤6.5% • Body weight loss ≥5% • Body weight loss ≥10% • Composite: HbA_{1c} <7% without hypoglycemia and no weight gain • Composite: HbA_{1c} reduction ≥1% and body weight loss ≥3%	The odds ratio between treatments in reaching target

BMI, body mass index; HOMA-B, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; SMBG, self-monitored blood glucose.
* Confirmatory endpoint at week 26.

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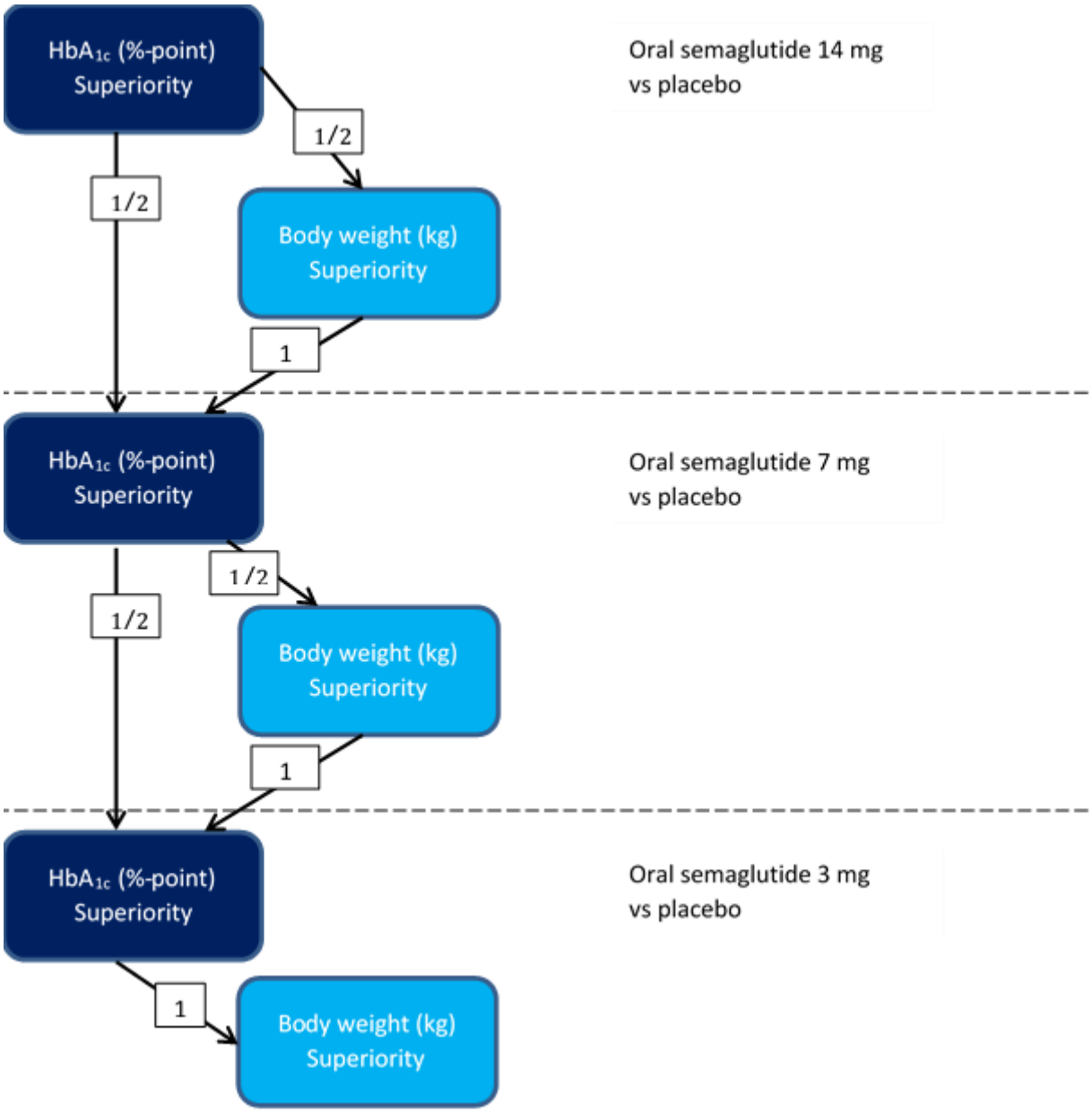
Supplementary Appendix 3. Statistical considerations.

The overall significance level of $\alpha = 0.05$ (two-sided) was initially allocated to the HbA_{1c} superiority test on the highest dose level (Figure). The local significance level (α-local) was then reallocated if a hypothesis was confirmed according to the weight given by the directed edges between nodes (hypotheses). The sample size was based on the hypotheses in the dark boxes. Multiplicity was controlled for the treatment policy estimand only.

Figure. Graphical illustration of the closed-testing procedure.



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The treatment policy estimand was estimated by a pattern mixture model using multiple imputation to handle missing data at week 26 for all continuous endpoints. All data collected at week 26 irrespectively of discontinuation of trial product and initiation of rescue medication were included in the statistical analysis. Imputation of missing data at week 26 was done within groups defined by randomized treatment and treatment status at week 26. The imputation model was an analysis of covariance (ANCOVA) with region as factor and baseline value as covariate. One thousand complete data sets were generated and analyzed separately by an ANCOVA with treatment and region as factors and baseline value as covariate. The estimated means and variances were combined by use of Rubin's rule[2] to draw inference.

The trial product estimand was estimated by a mixed model for repeated measurements (MMRM). A restricted maximum likelihood was used. The model included all post-baseline measurements collected at scheduled visits up to and including week 26 as dependent variable. The independent effects included in the model were treatment and region as categorical fixed effects and baseline value as a covariate, all nested within visit. An unstructured covariance matrix for endpoint measurements within the same patient was employed. For patients who did not have post-baseline assessments for planned visits available in the on-treatment without rescue medication period, the baseline value was carried forward to the first planned visit to ensure that all randomized patients contributed to the statistical analysis.

Supportive binary endpoints were analyzed by a logistic regression model. For the treatment policy estimand, missing data were imputed similarly as for the continuous endpoints, whereas missing data for the trial product estimand were imputed from patients randomized to same trial product using a sequential multiple imputation method.

All analyses were performed using SAS Version 9.4M2.

The safety analysis set comprised all randomised subjects who received at least one dose of trial product. Subjects contribute to a treatment group based on the trial product they actually received for the majority of the on-treatment observation period.

In-trial: The period where the patient is considered to be in the trial regardless of trial product discontinuation.

On-treatment: The period where the patient is considered treated with trial product.

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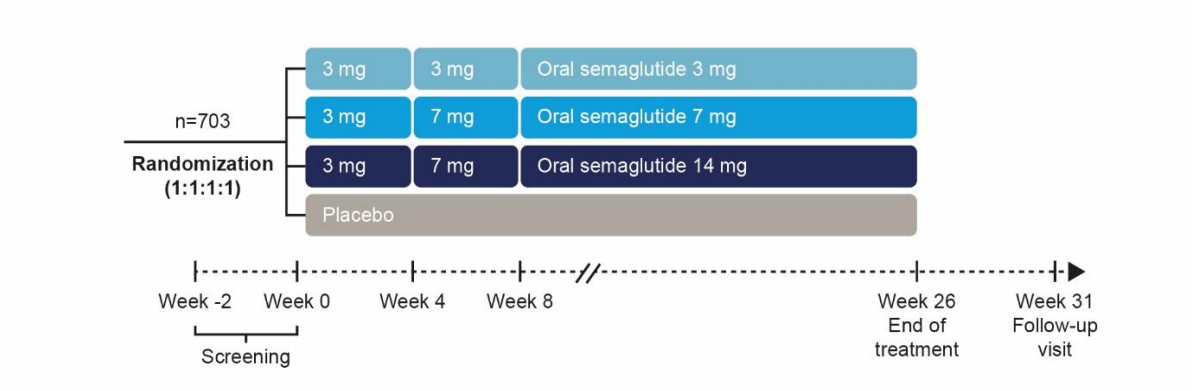
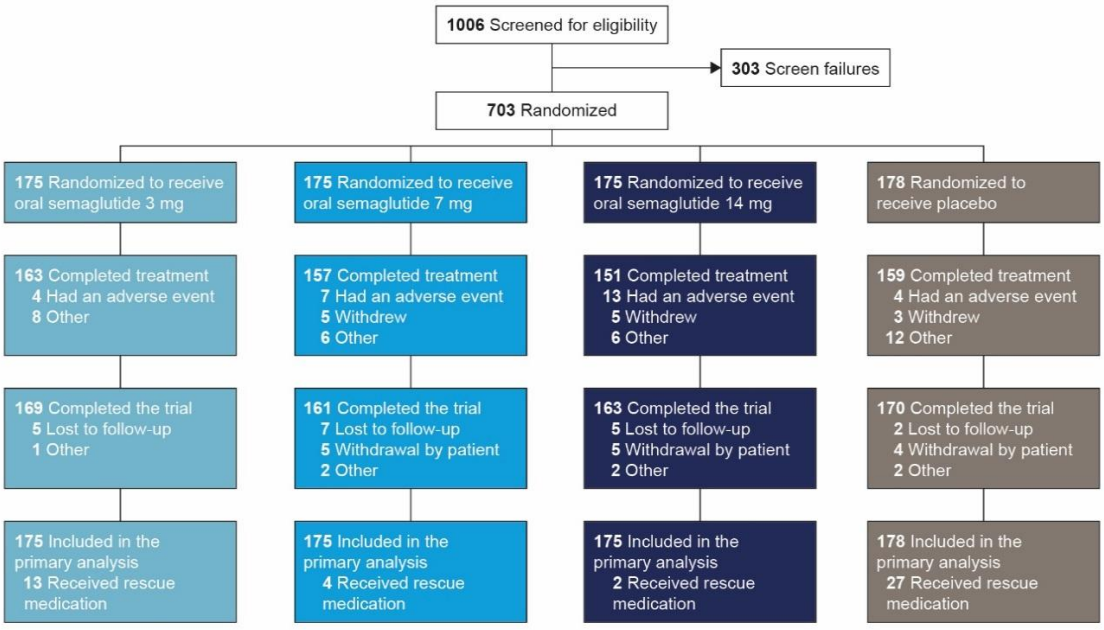
Supplementary Figure 1. Trial design.



All patients randomized to oral semaglutide initiated treatment with 3 mg once daily and followed a fixed 4-week dose-escalation regimen until reaching the maximum randomized dose.

Supplementary Figure 2. Flow of patients through the PIONEER 1 trial.



The primary 'other' reason provided for withdrawing from the study was protocol violation.
FAS, full analysis set.

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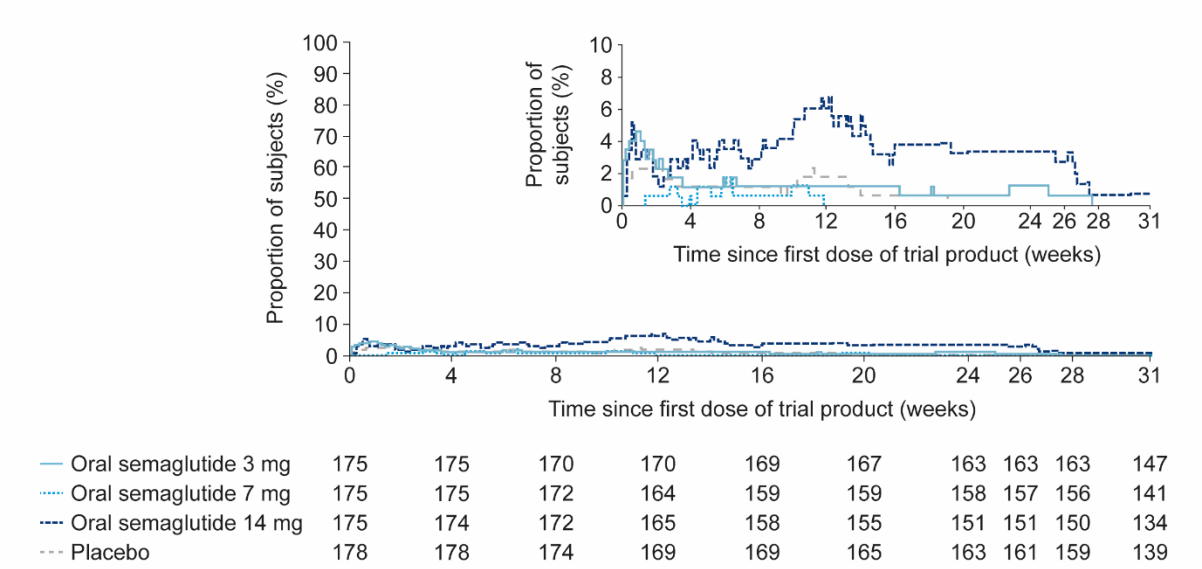
Supplementary Figure 3. Overview of nausea events on treatment.



The figure shows the proportion of patients with nausea events during the course of the trial. The inset figure are the same data but with the axis truncated to allow better visualization of the data.

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Supplementary Table 1. List of inclusion and exclusion criteria.

Key inclusion criteria
• Informed consent
• Male or female, age ≥18 years (Japan ≥20 years, Algeria ≥19 years)
• Diagnosed with type 2 diabetes mellitus and on treatment with diet/exercise for at least 30 days before screening
• Glycated hemoglobin 7.0–9.5% (both inclusive)
Key exclusion criteria
• Treatment with glucose-lowering agent in 90 days prior to screening (short-term [≤14 days]) insulin treatment excepted)
• History of pancreatitis
• Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
• Estimated glomerular filtration rate <60 mL/min/1.73 m^2
• Acute coronary or cerebrovascular event within 180 days before randomization
• Heart failure New York Heart Association class IV
• Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomization
• Malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas)

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Supplementary Table 2. Rescue medication and additional glucose-lowering medication use.

	Oral semaglutide 3 mg (n = 175)	**Oral semaglutide 7 mg (n = 175)**	**Oral semaglutide 14 mg (n = 175)**	**Placebo (n = 178)**
No. of patients (%) on rescue medication*	**13 (7.4)**	**4 (2.3)**	**2 (1.1)**	**27 (15.2)**
Biguanides	9 (5.1)	2 (1.1)	2 (1.1)	20 (11.2)
Sulfonylureas	2 (1.1)	1 (0.6)	0	7 (3.9)
Insulins, long-acting	3 (1.7)	0	0	2 (1.1)
SGLT2 inhibitors	1 (0.6)	1 (0.6)	0	2 (1.1)
Insulins, intermediate-acting	0	0	0	1 (0.6)
Thiazolidinediones	1 (0.6)	0	0	0
No. of patients (%) on additional glucose-lowering medication†	**16 (9.1)**	**8 (4.6)**	**7 (4.0)**	**35 (19.7)**
Biguanides	12 (6.9)	6 (3.4)	6 (3.4)	25 (14.0)
Sulfonylureas	2 (1.1)	1 (0.6)	2 (1.1)	8 (4.5)
Insulins, long-acting	4 (2.3)	0	0	3 (1.7)
SGLT2 inhibitors	1 (0.6)	1 (0.6)	0	2 (1.1)
DPP-4 inhibitors	0	0	0	2 (1.1)
Insulins, fast-acting	1 (0.6)	0	0	0
Insulins, intermediate-acting	0	0	0	1 (0.6)
Thiazolidinediones	1 (0.6)	0	0	0

DPP, dipeptidyl peptidase; SGLT, sodium-glucose cotransporter.

* Initiated after randomization and before last day on trial product.

† Initiated after randomization and before planned end of treatment. Additional glucose-lowering medication included 1) the use of rescue medication, and/or 2) the use of glucose-lowering medication for patients who discontinued trial product but remained in the trial.

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Supplementary Table 3. Secondary endpoints at week 26 not included in the main text.

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide 3 mg (n = 175)	**Oral semaglutide 7 mg (n = 175)**	**Oral semaglutide 14 mg (n = 175)**	**Placebo (n = 178)**	**Oral semaglutide 3 mg (n = 175)**	**Oral semaglutide 7 mg (n = 175)**	**Oral semaglutide 14 mg (n = 175)**	**Placebo (n = 178)**
Week 26: Proportion of patients (%) achieving:								
Body weight loss ≥10%	2.4	8.1	14.4	1.2	2.7	8.7	15.4	1.5
Odds ratio [95% CI] vs placebo	1.88 [0.34 to 10.44]	7.74 [1.68 to 35.72]	12.92 [2.98 to 56.07]	–	1.44 [0.27 to 7.63]	5.26 [1.22 to 22.72]	10.89 [2.63 to 44.98]	–
P value	0.47	0.009	<0.001	–	0.67	0.03	0.001	–
Body mass index (kg/m^2)								
Estimated mean at week 26	31.3	31.0	30.4	31.3	31.2	30.9	30.3	31.3
Mean change from baseline	–0.5	–0.8	–1.4	–0.5	–0.6	–0.9	–1.5	–0.5
Estimated treatment difference vs placebo [95% CI]	–0.1 [–0.3 to 0.2]	–0.3 [–0.7 to –0.0]	–0.9 [–1.2 to –0.6]	–	–0.1 [–0.4 to 0.2]	–0.4 [–0.7 to –0.1]	–1.0 [–1.3 to –0.7]	–
P value	0.74	0.05	<0.001	–	0.60	0.01	<0.001	–
Fasting pro-insulin (pmol/L)								
Estimated geometric mean at week 26	22.7	19.9	17.6	23.8	21.7	18.9	15.7	23.6
Ratio to baseline	0.84	0.74	0.65	0.89	0.84	0.73	0.61	0.92
Estimated treatment ratio vs placebo [95% CI]	0.95 [0.83 to 1.09]	0.83 [0.71 to 0.98]	0.74 [0.64 to 0.85]	–	0.92 [0.79 to 1.07]	0.80 [0.69 to 0.93]	0.67 [0.57 to 0.77]	–
P value	0.48	0.03	<0.001	–	0.26	0.003	<0.001	–
Fasting glucagon (pg/mL)								
Estimated geometric mean at week 26	86	80	78	82	85	78	77	80
Ratio to baseline	0.99	0.92	0.90	0.95	0.99	0.91	0.90	0.93
Estimated treatment ratio vs placebo [95% CI]	1.04 [0.99 to 1.10]	0.97 [0.91 to 1.03]	0.94 [0.89 to 1.00]	–	1.07 [1.01 to 1.13]	0.97 [0.92 to 1.03]	0.96 [0.91 to 1.02]	–
P value	0.13	0.32	0.05	–	0.03	0.37	0.21	–
HOMA-IR (%)								
Estimated geometric mean at week 26	4.6	4.0	3.6	4.2	4.3	4.0	3.4	4.1
Ratio to baseline	1.01	0.88	0.78	0.93	0.97	0.89	0.76	0.92
Estimated treatment ratio vs	1.09 [0.96 to	0.95 [0.83 to	0.84 [0.74 to	–	1.05 [0.92 to	0.97 [0.85 to	0.82 [0.72 to	–

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide 3 mg (n = 175)	**Oral semaglutide 7 mg (n = 175)**	**Oral semaglutide 14 mg (n = 175)**	**Placebo (n = 178)**	**Oral semaglutide 3 mg (n = 175)**	**Oral semaglutide 7 mg (n = 175)**	**Oral semaglutide 14 mg (n = 175)**	**Placebo (n = 178)**
placebo [95% CI]	1.24]	1.09]	0.95]		1.20]	1.11]	0.93]	
P value	0.18	0.48	0.007	–	0.44	0.66	0.003	–
Fasting C-peptide (ng/mL)								
Estimated geometric mean at week 26	2.896	2.860	2.787	2.634	2.870	2.883	2.747	2.607
Ratio to baseline	1.09	1.08	1.05	0.99	1.09	1.10	1.05	0.99
Estimated treatment ratio vs placebo [95% CI]	1.10 [1.02 to 1.18]	1.09 [1.01 to 1.17]	1.06 [0.98 to 1.14]	–	1.10 [1.02 to 1.19]	1.11 [1.02 to 1.20]	1.05 [0.97 to 1.14]	–
P value	0.01	0.04	0.13	–	0.02	0.01	0.19	–
Fasting insulin (pmol/L)								
Estimated geometric mean at week 26	98	91	85	83	92	92	83	80
Ratio to baseline	1.15	1.07	0.99	0.97	1.08	1.08	0.97	0.94
Estimated treatment ratio vs placebo [95% CI]	1.18 [1.06 to 1.32]	1.10 [0.97 to 1.24]	1.02 [0.92 to 1.13]	–	1.15 [1.04 to 1.28]	1.15 [1.03 to 1.28]	1.03 [0.93 to 1.15]	–
P value	0.003	0.13	0.73	–	0.009	0.01	0.53	–
HOMA-B (%)								
Estimated geometric mean at week 26	69.8	73.6	76.8	49.1	66.2	77.7	81.4	47.6
Ratio to baseline	1.44	1.51	1.58	1.01	1.33	1.56	1.63	0.96
Estimated treatment ratio vs placebo [95% CI]	1.42 [1.24 to 1.63]	1.50 [1.28 to 1.76]	1.56 [1.37 to 1.79]	–	1.39 [1.23 to 1.57]	1.63 [1.44 to 1.85]	1.71 [1.51 to 1.93]	–
P value	<0.001	<0.001	<0.001	–	<0.001	<0.001	<0.001	–
C-reactive protein (mg/L)								
Estimated geometric mean at week 26	2.45	2.08	1.96	2.81	2.42	2.02	2.12	2.77
Ratio to baseline	0.88	0.74	0.70	1.01	0.86	0.72	0.76	0.99
Estimated treatment ratio vs placebo [95% CI]	0.87 [0.71 to 1.06]	0.74 [0.60 to 0.91]	0.70 [0.52 to 0.92]	–	0.87 [0.72 to 1.06]	0.73 [0.60 to 0.89]	0.76 [0.63 to 0.93]	–
P value	0.17	0.004	0.01		0.17	0.002	0.008	–
Total cholesterol (mg/dL)								
Estimated geometric mean at week 26	186	188	180	188	186	187	182	190

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide 3 mg (n = 175)	**Oral semaglutide 7 mg (n = 175)**	**Oral semaglutide 14 mg (n = 175)**	**Placebo (n = 178)**	**Oral semaglutide 3 mg (n = 175)**	**Oral semaglutide 7 mg (n = 175)**	**Oral semaglutide 14 mg (n = 175)**	**Placebo (n = 178)**
Ratio to baseline	0.98	0.99	0.95	1.00	0.98	0.99	0.96	1.00
Estimated treatment ratio vs placebo [95% CI]	0.99 [0.95 to 1.02]	1.00 [0.95 to 1.04]	0.95 [0.92 to 0.99]	–	0.98 [0.95 to 1.02]	0.99 [0.95 to 1.02]	0.96 [0.92 to 0.99]	–
P value	0.48	0.85	0.02	–	0.28	0.50	0.02	–
Low-density lipoprotein cholesterol (mg/dL)								
Estimated geometric mean at week 26	104	106	101	108	104	107	103	109
Ratio to baseline	0.95	0.98	0.93	0.99	0.95	0.98	0.94	1.00
Estimated treatment ratio vs placebo [95% CI]	0.97 [0.91 to 1.03]	0.99 [0.92 to 1.06]	0.94 [0.89 to 1.00]	–	0.95 [0.90 to 1.01]	0.98 [0.92 to 1.04]	0.94 [0.89 to 1.00]	–
P value	0.25	0.74	0.05	–	0.10	0.45	0.03	–
High-density lipoprotein cholesterol (mg/dL)								
Estimated geometric mean at week 26	45	46	45	45	45	46	45	46
Ratio to baseline	1.03	1.05	1.02	1.03	1.03	1.04	1.02	1.04
Estimated treatment ratio vs placebo [95% CI]	1.00 [0.97 to 1.03]	1.03 [0.99 to 1.06]	1.00 [0.97 to 1.03]	–	0.99 [0.96 to 1.02]	1.00 [0.97 to 1.03]	0.98 [0.95 to 1.01]	–
P value	0.83	0.10	0.88	–	0.55	0.92	0.23	–
Triglycerides (mg/dL)								
Estimated geometric mean at week 26	154	141	137	152	157	142	141	148
Ratio to baseline	1.01	0.92	0.90	0.99	1.02	0.92	0.92	0.97
Estimated treatment ratio vs placebo [95% CI]	1.02 [0.94 to 1.10]	0.93 [0.84 to 1.02]	0.90 [0.83 to 0.99]	–	1.06 [0.98 to 1.14]	0.95 [0.88 to 1.03]	0.95 [0.88 to 1.03]	–
P value	0.71	0.13	0.02	–	0.18	0.24	0.24	–

CI, confidence interval; CV, coefficient of variation; HOMA-B, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

Baseline levels (geometric mean [CV] for the total population unless otherwise specified) were: fasting insulin, 85.6 (100.2) pmol/L; fasting pro-insulin, 26.9 (121.7) pmol/L; fasting glucagon, 86.7 (34.0) pg/mL; HOMA IR, 4.55 (108.01)%; HOMA-B, 48.59 (119.75)%; C-peptide, 0.88 (49.51) ng/mL; C-reactive protein, 2.80 (178.14) mg/L; total cholesterol, 189.1 (21.6) mg/dL; low-density lipoprotein cholesterol, 109.0 (31.1) mg/dL; high-density lipoprotein cholesterol, 44.2 (26.4) mg/dL; triglycerides, 153.0 (61.9) mg/dL. Data reported in the main baseline characteristic table are not duplicated in

this table. Data reported are the estimated values, except for the proportions of patients achieving targets or composite endpoints.

P values less than 0.001 are reported as "*P*<0.001". *P* values between 0.001 and 0.01 are reported to the nearest thousandth and *P* values greater than or equal to 0.01 are reported to the nearest hundredth.

Treatment policy estimand: Analysis of covariance (ANCOVA) for continuous endpoints and logistic regression for binary endpoints, using data irrespective of discontinuation of trial product and initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation (MI). Patterns were defined by use of trial product and rescue medication.

Trial product estimand: Mixed model for repeated measurements (MMRM) for continuous endpoints and logistic regression for binary endpoints. Data collected after discontinuation of trial product and initiation of rescue medication were excluded. For binary endpoints, missing values were imputed from subjects randomized to same trial product using sequential MI.

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Supplementary Table 4. On-treatment adverse events leading to discontinuation by system organ class/preferred term.

	Oral semaglutide 3 mg (n = 175)	**Oral semaglutide 7 mg (n = 175)**	**Oral semaglutide 14 mg (n = 175)**	**Placebo (n = 178)**
	No. of patients (%) with at least one event			
Adverse events leading to premature trial product discontinuation, * no. of patients (%)	4 (2.3)	7 (4.0)	13 (7.4)	4 (2.2)
Gastrointestinal disorders	3 (1.7)	4 (2.3)	9 (5.1)	1 (0.6)
Abdominal pain upper	0	1 (0.6)	3 (1.7)	1 (0.6)
Constipation	0	1 (0.6)	2 (1.1)	0
Diarrhea	0	1 (0.6)	2 (1.1)	0
Nausea	2 (1.1)	2 (1.1)	2 (1.1)	0
Abdominal discomfort	0	0	1 (0.6)	0
Abdominal distension	1 (0.6)	0	1 (0.6)	0
Defecation urgency	0	0	1 (0.6)	0
Gastroesophageal reflux disease	1 (0.6)	1 (0.6)	1 (0.6)	0
Vomiting	0	2 (1.1)	1 (0.6)	0
Abdominal pain	1 (0.6)	2 (1.1)	0	0
Pancreatitis acute	1 (0.6)	0	0	0
Investigations	0	0	3 (1.7)	0
Amylase increased	0	0	1 (0.6)	0
Lipase increased	0	0	1 (0.6)	0
Pancreatic enzymes increased	0	0	1 (0.6)	0
Weight decreased	0	0	1 (0.6)	0
Metabolism and nutrition disorders	0	0	3 (1.7)	0
Decreased appetite	0	0	3 (1.7)	0
General disorders and administration site conditions	0	1 (0.6)	1 (0.6)	0
Asthenia	0	0	1 (0.6)	0
Malaise	0	1 (0.6)	0	0
Infections and infestations	0	0	1 (0.6)	0
Influenza	0	0	1 (0.6)	0
Nervous system disorders	0	0	1 (0.6)	2 (1.1)
Headache	0	0	1 (0.6)	0
Cerebral infarction	0	0	0	1 (0.6)
Presyncope	0	0	0	1 (0.6)
Ear and labyrinth disorders	0	1 (0.6)	0	0
Vertigo	0	1 (0.6)	0	0
Neoplasms benign, malignant, and unspecified	1 (0.6)	0	0	0
Papillary thyroid cancer	1 (0.6)	0	0	0
Respiratory, thoracic, mediastinal disorders	0	0	0	1 (0.6)
Pulmonary embolism	0	0	0	1 (0.6)
Skin and subcutaneous tissue disorders	0	1 (0.6)	0	1 (0.6)
Dermatitis, allergic	0	0	0	1 (0.6)

Eczema	0	1 (0.6)	0	0
Vascular disorders	0	0	0	1 (0.6)
Shock	0	0	0	1 (0.6)

* Patients could experience multiple events.
On treatment: The period where the patient is considered treated with trial product.

Supplementary Table 5. External adjudication committee-confirmed events and selected in-trial adverse events.

Preferred term	Oral semaglutide 3 mg (n = 175)	Oral semaglutide 7 mg (n = 175)	Oral semaglutide 14 mg (n = 175)	Placebo (n = 178)
	No. of patients (%) with at least one event			
In-trial events				
Deaths	0	0	1 (0.6)	0
Cardiovascular disorders*	3 (1.7)	5 (2.9)	2 (1.1)	5 (2.8)
Serious	1 (0.6)	0	2 (1.1)	4 (2.2)
Neoplasms*	3 (1.7)	2 (1.1)	1 (0.6)	9 (5.1)
Malignant	1 (0.6)	0	0	3 (1.7)
Events confirmed by the external adjudication committee				
Death				
On treatment	0	0	0	0
In trial	0	0	1 (0.6)	0
Acute kidney injury				
On treatment	0	0	1 (0.6)	1 (0.6)
In trial	0	0	1 (0.6)	1 (0.6)
Acute pancreatitis				
On treatment	0	0	0	0
In trial	0	0	0	0
Cardiovascular events				
On treatment	0	0	1 (0.6)	2 (1.1)
In trial	0	0	2 (1.1)	2 (1.1)
Acute coronary syndrome				
On treatment	0	0	1 (0.6)	0
In trial	0	0	1 (0.6)	0
Cerebrovascular events				
On treatment	0	0	0	2 (1.1)
In trial	0	0	0	2 (1.1)
Heart failure requiring hospitalization				
On treatment	0	0	0	0
In trial	0	0	0	0
Malignant neoplasms†				
On treatment	1 (0.6)	0	0	3 (1.7)
In trial	1 (0.6)	0	0	3 (1.7)
Thyroid-related events‡				

On treatment	0	0	0	0
In trial	0	0	0	0
Lactic acidosis				
On treatment	0	0	0	0
In trial	0	0	0	0

* Pre-defined Medical Dictionary for Regulatory Activities (Version 20.1) search.
† Excludes malignant thyroid neoplasms.
‡ Includes malignant thyroid neoplasms.
In trial: The period where the patient is considered to be in the trial regardless of trial product discontinuation.
On treatment: The period where the patient is considered treated with trial product.

Supplementary Table 6. In-trial adverse events related to diabetic retinopathy identified using medical dictionary for regulatory activities (version 20.1) terms.

Preferred term	Oral semaglutide 3 mg (n = 175)	Oral semaglutide 7 mg (n = 175)	Oral semaglutide 14 mg (n = 175)	Placebo (n = 178)
	No. of patients (%) with at least one event			
Diabetic retinopathy	1 (0.6)	6 (3.4)	2 (1.1)	3 (1.7)
Vitreous detachment	0	0	0	1 (0.6)

In trial: The period where the patient is considered to be in the trial regardless of trial product discontinuation.

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Supplementary Table 7. Additional safety parameters at week 26.

	In trial				On treatment			
	Oral semaglutide 3 mg (n = 175)	**Oral semaglutide 7 mg (n = 175)**	**Oral semaglutide 14 mg (n = 175)**	**Placebo (n = 178)**	**Oral semaglutide 3 mg (n = 175)**	**Oral semaglutide 7 mg (n = 175)**	**Oral semaglutide 14 mg (n = 175)**	**Placebo (n = 178)**
Systolic blood pressure (mmHg)								
Estimated mean at week 26	126	127	125	127	126	126	125	127
Mean change from baseline	–3	–3	–5	–3	–4	–4	–5	–2
Estimated treatment difference vs placebo [95% CI]	–1 [–4 to 2]	–1 [–4 to 2]	–2 [–5 to 0]	–	–1 [–4 to 2]	–1 [–4 to 1]	–2 [–5 to 0]	–
P value	0.55	0.68	0.10	–	0.44	0.29	0.07	–
Diastolic blood pressure (mmHg)								
Estimated mean at week 26	79	79	78	79	79	78	78	79
Mean change from baseline	–1	–1	–1	–1	–1	–1	–1	–1
Estimated treatment difference vs placebo [95% CI]	0 [–2 to 2]	–0 [–2 to 2]	–0 [–2 to 1]	–	–0 [–2 to 1]	–1 [–2 to 1]	–1 [–2 to 1]	–
P value	0.91	0.91	0.68	–	0.86	0.49	0.49	–
Pulse rate (beats per minute)								
Estimated mean at week 26	73	74	76	73	73	74	76	73
Mean change from baseline	0	1	3	–0	0	1	3	–0
Estimated treatment difference vs placebo [95% CI]	1 [–1 to 2]	1 [–1 to 3]	3 [1 to 5]	–	1 [–1 to 2]	1 [–1 to 3]	3 [2 to 5]	–
P value	0.45	0.35	0.003	–	0.55	0.27	<0.001	–
Lipase (U/L)								
Estimated geometric mean at week 26	32	35	36	28	32	36	38	28
Ratio to baseline	1.14	1.24	1.28	0.99	1.12	1.27	1.33	0.99
Estimated treatment ratio vs placebo [95% CI]	1.15 [1.04 to 1.26]	1.25 [1.13 to 1.38]	1.29 [1.16 to 1.43]	–	1.13 [1.04 to 1.24]	1.28 [1.17 to 1.40]	1.34 [1.22 to 1.47]	–
P value	0.004	<0.001	<0.001	–	0.007	<0.001	<0.001	–
Amylase (U/L)								
Estimated geometric mean at week 26	52	54	55	49	52	55	56	49
Ratio to baseline	1.04	1.07	1.11	0.98	1.04	1.10	1.12	0.98
Estimated treatment ratio vs	1.07 [1.02 to	1.09 [1.04 to	1.13 [1.07 to 1.19]	–	1.06 [1.01 to	1.12 [1.06 to	1.14 [1.09 to 1.19]	–

placebo [95% CI]	1.12]	1.15]			1.11]	1.17]		
P value	0.008	0.001	<0.001	–	0.015	<0.001	<0.001	–
Estimated glomerular filtration rate ratio to baseline								
Geometric mean (CV) at week 26					0.99 (10.7)	1.00 (9.6)	1.00 (8.2)	1.00 (8.9)
Occurrence of anti-semaglutide antibodies at any post-baseline visit, n (%)					2 (1.2)*	1 (0.6)	0 (0.0)	0 (0.0)

CV, coefficient of variation; CI, confidence interval; SD, standard deviation.

Total mean (SD) baseline values were: systolic blood pressure, 129.9 (14.4) mmHg; diastolic blood pressure, 79.8 (9.4) mmHg; pulse rate 72.9 (10.3) beats per minute. Total geometric mean (CV) values were: amylase, 50.1 (43.6) U/L; lipase, 28.5 (97.5) U/L, estimated glomerular filtration rate 96.4 (15.6) mL/min/1.73m^2.

*Antibodies were neutralizing in n=1 patient at one visit

P values less than 0.001 are reported as "*P*<0.001". *P* values between 0.001 and 0.01 are reported to the nearest thousandth and *P* values greater than or equal to 0.01 are reported to the nearest hundredth.

In trial: The period where the patient is considered to be in the trial regardless of trial product discontinuation. Analysis of covariance (ANCOVA) for continuous endpoints and logistic regression for binary endpoints, using data irrespective of discontinuation of trial product and initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation (MI). Patterns were defined by use of trial product and rescue medication.

On treatment: The period where the patient is considered treated with trial product. Mixed model for repeated measurements (MMRM) for continuous endpoints. Data collected after discontinuation of trial product was excluded. For binary endpoints, missing values were imputed from subjects randomized to same trial product using sequential MI.

SUPPLEMENTARY DATA

Online-only references

1. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Estimands and sensitivity analysis in clinical trials E9 (R1). 2017. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Step2_Guideline_2017_0616.pdf. Accessed November 14, 2018.
2. Little RJA, Rubin DB. *Statistical analysis with missing data*. New York, NY. John Wiley and Sons; 1987.