1 Summary

Objectives and endpoints:

Primary objective

To compare the effect of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without sulfonylurea (SU), on glycaemic control in subjects with type 2 diabetes mellitus (T2DM).

Secondary objectives

To compare the effect of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, on body weight in subjects with T2DM.

To compare the long-term safety and tolerability of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without SU, in subjects with T2DM.

Primary endpoint

Change from baseline to week 26 in HbA_{1c}

Key secondary endpoints

Change from baseline to week 26 in
- Body weight (kg)
- Fasting plasma glucose (FPG)

Subjects who after 26 weeks of treatment achieve (yes/no):
- $HbA_{1c} < 7.0\%$ (53 mmol/mol), American Diabetes Association (ADA) target
  This endpoint will also be evaluated after week 52 and after week 78.

Change from baseline to week 52 and to week 78 in:
- HbA_{1c}
- Body weight (kg)
- FPG

Number of treatment emergent adverse events (TEAEs) during exposure to trial product, assessed up to approximately 83 weeks

Number of treatment emergent severe or blood glucose (BG) confirmed symptomatic hypoglycaemic episodes during exposure to trial product, assessed up to approximately 83 weeks

Trial design:

The trial is a 78 week, randomised, double-blind, double-dummy, active-controlled, parallel-group, multi-centre, multi-national, four-armed trial.

Subjects with T2DM inadequately controlled with metformin or metformin + sulfonylurea (SU) will be randomised in a 1:1:1:1 manner to receive either a dose of 3 mg, 7 mg or 14 mg of oral semaglutide once-daily or a dose of 100 mg sitagliptin once-daily.

Total trial duration for the individual subject will be approximately 85 weeks. The trial includes a 2 week screening period, followed by a 78 week randomised treatment period and a follow-up period of 5 weeks.

Trial population:

It is planned to randomise 1860 subjects.

Key inclusion criteria

- Male or female, age ≥ 18 years at the time of signing informed consent.
  For Japan only: Male or female, age ≥ 20 years at the time of signing informed consent.
- Diagnosed with T2DM ≥ 90 days prior to day of screening.
- HbA_{1c} 7.0-10.5 % (53-91 mmol/mol) (both inclusive).
- Stable daily dose of metformin (≥ 1500 mg or maximum tolerated dose as documented in subject medical record) alone or in combination with SU (≥ half of the maximum approved dose according to local label or maximum tolerated dose as documented in subject medical record) within 90 days prior to the day of screening.

Key exclusion criteria

- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
  For certain specific countries: Additional specific requirements apply.
- Family or personal history of Multiple Endocrine Neoplasia Type 2 (MEN 2) or Medullary Thyroid Carcinoma (MTC).
- History of pancreatitis (acute or chronic).
- History of major surgical procedures involving the stomach potentially affecting absorption of trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery).
- Any of the following: myocardial infarction, stroke or hospitalization for unstable angina and/or transient ischaemic attack within the past 180 days prior to the day of screening.
- Subjects presently classified as being in New York Heart Association (NYHA) Class IV.
- Planned coronary, carotid or peripheral artery revascularisation known on the day of screening.
- Renal impairment defined as estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73 m^2 as per Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).
- History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas).

Key assessments:

Efficacy:

- HbA_{1c}
- FPG
- Body weight

Safety:

- Adverse events
- Hypoglycaemic episodes

Trial products:

The following trial products will be supplied by Novo Nordisk A/S, Denmark:

- Semaglutide, 3 mg tablet
- Semaglutide, 7 mg tablet
- Semaglutide, 14 mg tablet
- Semaglutide placebo tablet (Placebo I)
- Sitagliptin (Januvia®), 100 mg tablet
- Sitagliptin placebo tablet (Placebo II)

2 Flow chart

Trial Periods	Screening[1]	Randomisation	Treatment													End-of-treatment (EoT)	Follow-up[2]	EoT premature discontinuation[3]	Follow-up premature discontinuation[3]
Visit (V), Phone (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V16A	V17A
Timing of visit (weeks)	Up to -2 wks	0	2	4	8	14	20	26	32	38	45	52	59	66	72	78	83	Shortly after discontinua-tion of trial product	5 weeks after discontinua-tion of trial product (last dose)
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3		+3
SUBJECT RELATED INFO/ASSESSMENTS																			
Informed consent	x																		
In/exclusion criteria	x	x																	
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography	x																		
Tobacco use	x																		
Concomitant illness and medical history	x																		
History of diabetes	x																		
History of cardiovascular disease	x																		
History of gallbladder disease	x																		
History of gastrointestinal disease	x																		
Randomisation		x																	
Withdrawal criteria			x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	

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Visit (V), Phone (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V16A	V17A
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Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3		+3
EFFICACY																			
HbA_{1c}	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Fasting plasma glucose		x		x	x	x	x	x		x		x		x		x		x	
PK Sampling[4]		x		x	x	x		x		x		x				x	x	x	x
Lipids		x						x				x				x		x	
Body height		x																	
Body weight, BMI		x		x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Waist circumference		x				x		x		x		x		x		x		x	
7-point profile		x						x				x				x		x	
PRO questionnaires		x						x				x				x		x	
SAFETY																			
Eye examination[5]	x																		
Physical examination	x											x				x		x	
Electrocardiogram		x						x				x				x	x	x	x
Vital signs		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test[6]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Calcitonin		x				x		x		x		x		x		x	x	x	x
Biochemistry[7]	x	x		x	x	x		x		x		x		x		x	x	x	x
Haematology		x		x	x	x		x		x		x		x		x	x	x	x

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Visit (V), Phone (P)	V1	V2	P3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V16A	V17A
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Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+3		+3
Antibodies[8]		x		x	x	x		x		x		x				x	x	x	x
Adverse events[9]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hypoglycaemic episodes		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Technical complaints			x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	
TRIAL MATERIAL																			
IWRS call	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x		x	
Dispensing of trial product		x		x	x	x	x	x	x	x	x	x	x	x	x				
Drug accountability				x	x	x	x	x	x	x	x	x	x	x	x	x		x	
REMINDERS																			
Hand out ID card	x																		
Hand out and instruct in BG meter use	x																		
Dispense and/or collect diary	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Attend visit fasting[10]		x		x	x	x	x	x		x		x		x		x		x	

Footer	Description
X[1]	Subject can be randomised as soon as all inclusion and exclusion criteria are confirmed. The screening assessments must not exceed 2 weeks prior to randomisation (V2).
X[2]	Subjects, who have discontinued trial product prematurely, are not required to attend V17 (Follow-up).
X[3]	V16A and V17A are only applicable for subjects who have discontinued trial product prematurely.
X[4]	PK sampling is only applicable for a subset of the subjects. No PK sampling should be done for visits occurring after V17A (subjects who have discontinued trial product prematurely).
X[5]	Dilated fundoscopy/fundus photography performed within 90 days prior to randomisation is acceptable if results are available for evaluation at V2, unless worsening of visual function since last examination.
X[6]	For women of child bearing potential: Urine pregnancy test should also be performed at any time during the trial if a menstrual period is missed and/or according to local regulations/law.
X[7]	At V1 only Creatinine and eGFR will be assessed as part of Biochemistry.
X[8]	At randomisation, the antibody sampling must be done pre-dose. No antibody sampling should be done for visits occurring after V17A (subjects who have discontinued trial product prematurely).
X[9]	Adverse events reporting, includes adverse events from the first trial-related activity after the subject has signed the informed consent at V1.
X[10]	Fasting for blood sampling is defined as having consumed only water within the last 8 hours prior to visit.