Supplementary materials to *BMJ Open* article

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Impact of patient characteristics on efficacy and safety of OW semaglutide vs dulaglutide: SUSTAIN 7 *post hoc* analyses

Authors:

Pratley Richard E[1], Aroda Vanita R[2], Catarig Andrei M[3], Lingvay Ildiko[4], Lüdemann Jörg[5], Yildirim Emre[6], Viljoen Adie[7]

Author affiliations:

[1]Translational Research Institute, AdventHealth, Orlando, FL, USA; [2]Division of Endocrinology, Diabetes & Hypertension, Brigham and Women's Hospital, Boston, MA, USA; [3]Medical and Science, Novo Nordisk A/S, Søborg, Denmark; [4]Department of Internal Medicine/Endocrinology and Department of Population and Data Sciences, University of Texas Southwestern Medical Center, Dallas, TX, USA; [5]diabetes-falkensee, Diabetes Centre and Centre for Clinical Studies, Falkensee, Germany; [6]Global Medical Affairs, Novo Nordisk A/S, Søborg, Denmark; [7]Borthwick Diabetes Research Centre, Lister Hospital, Stevenage, UK

Contact details for corresponding author:

Dr Richard E. Pratley
Translational Research Institute
AdventHealth
301 E. Princeton Street, Orlando, FL 32804, USA
Phone: +1-407-303-2519
E-mail: Richard.Pratley.MD@AdventHealth.com

SUPPLEMENTARY SECTION I: INDEPENDENT ETHICS COMMITTEES

Supplementary Table 1. Independent ethics committees for SUSTAIN 7

Country	Independent ethics committees
Bulgaria	• Ethics Committee for Multicenter Clinical Trials
Croatia	• Agencija za lijekove i medicinske proizvode
Finland	• Ethics Committee of the Hospital District of Southwest Finland
Germany	• Ethikkommission der Ärztekammer des Saarlandes
Greece	• National Ethics Committee • Private Clinic, Iatriko Palaiou Falirou • General Hospital of Thessaloniki "G. Papanikolaou" Exohi • General University Hospital of Chalkida • General Hospital of Piraeus "Tzaneio" 1 • "THERMI" Clinic 14th km of National Road Thessaloniki • General University Hospital of Thessaloniki "Ahepa" 1 • University Hospital of Ioannina • Private Clinic, Iatriko Psychikou 1
Hong Kong	• Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee
India	• Park Clinic Ethics Committee • Institutional Ethics Committee, Amrita Institute of Medical and Research Centre • Institutional Ethics Committee, Inamdar Multispeciality Hospital • IPGME&R Research Oversight Committee, Institute of Post-graduate Medical Education and Research • Institutional Ethics Committee, Deenanath Mangeshkar Hospital and Research Centre • Ethics Committee For Human Research, Lady Hardinge Medical College & Associated Hospitals • Institutional Human Ethics Committee, Office of the SOCOMER • Institutional Ethics Committee, Goa Medical College • Institutional Ethics Committee, Lokmanya Tilak Municipal Medical College • Ethics Committee, Apollo Hospital • Ethics Committee Silver, Christian Medical College • Ethics Committee, Endolife Speciality Hospitals Pvt. Ltd • Academic Research Projects, Medical College and BYL Nair Hospital • Institutional Ethics Committee, M/s. King George Hospital • Institutional Ethics Committee, Global Hospitals • Ethics Committee, Marwari Hospital & Research Center • Integrity Ethics Committee, Convenient Hospitals Ltd

	• Institutional Ethics Committee of Madras, Diabetes Research Foundation • The JMSHF and BMRC Institutional Ethics Committee, The Jivraj Mehta Hospital • Institutional Ethics Committee, Fortis Hospital • Institutional Ethics Committee, Maulana Azad Medical College • Drug Trial Ethics Committee, Dayanand Medical College and Hospital • Ethics Committee of Bangalore, Medical College & Research Institute • Institutional Ethics Committee, Osmania Medical College • Ethics Committee, Government Medical College • Institutional Ethics Committee, Postgraduate Institute of Medical Education & Research • Institute of Ethics Committee AIIMS
Ireland	• Clinical Research Ethics Committee of the Cork Teaching Hospitals • Mater Misericordiae Hospital • Galway University Hospital • Connolly Hospital • St Vincent's Healthcare Ethics and Medical Research Committee • The Palms Surgery
Latvia	• Ethics Committee for Clinical Research at Pauls Stradins Clinical University Hospital Development Society
Lithuania	• Lithuanian Bioethics Committee
Portugal	• Comissão de Ética para a Investigação Clínica
Romania	• National Bioethics Committee for Medicine and Medical Devices
Slovakia	• Eticka komisia, Sabinovska 16 • Eticka komisia, Nemocnica Svateho Michala, a.s. **(Central IEC)** • Eticka komisia, Trencianskeho samospravneho kraja • Eticka komisia, Nitrianskeho samospravneho kraja • Etická komisia, Presovskeho samospravneho kraja • Eticka komisia, Trnavskeho samospravneho kraja
Spain	• Comité Coordinador de Ética de la Investigación Biomédica de Andalucía • CEI Provincial de Málaga
UK	• NRES Committee East of England – Cambridge Central • Research and Development Department East and North Hertfordshire NHS Trust • RMG Office, NHS Cambridgeshire and Peterborough CCG • Clinical Research Network North Thames • East of England – Cambridge Central Research Ethics Committee • Room 4, 112, 1 West University of Bath

	• Research and Development Department Clinical Trial Facility, Moorgreen Hospital • R&D Department, University Hospital Southampton NHS Foundation Trust
USA	• Sterling Institutional Review Board • Western International Review Board • University of Texas Southwestern Medical Center Institutional Review Board • Schulman Associates IRB, Inc. • Florida Hospital Institutional Review Board

SUPPLEMENTARY SECTION II: BASELINE CHARACTERISTICS

Supplementary Table 2. Baseline characteristics by sex subgroups

		Male				Female			
	All subjects	**Sema 0.5 mg**	**Dula 0.75 mg**	**Sema 1.0 mg**	**Dula 1.5 mg**	**Sema 0.5 mg**	**Dula 0.75 mg**	**Sema 1.0 mg**	**Dula 1.5 mg**
n	**1,199**	**169**	**160**	**162**	**171**	**132**	**139**	**138**	**128**
Age, years	56 (10.6)	57.0 (10.9)	55.6 (10.1)	55.6 (10.3)	56.8 (10.5)	55.3 (10.9)	54.9 (10.7)	55.1 (11.0)	54.7 (10.7)
Sex, n (%)									
Male	662 (55.2)	169 (100)	160 (100)	162 (100)	171 (100)	-	-	-	-
Female	537 (44.8)	-	-	-	-	132 (100)	139 (100)	138 (100)	128 (100)
Diabetes duration, years	7.4 (5.7)	7.8 (5.8)	7.1 (5.7)	7.4 (5.5)	8.0 (5.6)	7.7 (6.1)	6.9 (5.2)	7.1 (5.9)	7.2 (5.7)
HbA_{1c}, %	8.2 (0.9)	8.4 (1.0)	8.2 (0.9)	8.2 (0.9)	8.2 (0.8)	8.3 (1.0)	8.1 (0.9)	8.2 (0.9)	8.2 (1.0)
HbA_{1c}, mmol/mol	66.4 (10.0)	67.8 (10.5)	66.2 (10.0)	66.0 (10.2)	65.8 (9.0)	67.1 (10.4)	66.4 (9.9)	65.2 (9.9)	66.6 (10.6)
Body weight, kg	95.2 (22.6)	102.3 (23.9)	100.6 (23.4)	100.8 (21.0)	96.9 (21.5)	88.9 (23.0)	89.9 (21.3)	89.3 (19.0)	88.8 (21.3)
BMI, kg/m^2	33.5 (6.8)	33.3 (6.8)	32.8 (6.6)	32.7 (6.2)	32.0 (5.8)	34.2 (7.5)	34.6 (7.2)	34.7 (6.7)	34.5 (7.2)
Race, n (%)									
Asian	191 (15.9)	24 (14.2)	31 (19.4)	25 (15.4)	32 (18.7)	26 (19.7)	17 (12.2)	13 (9.4)	23 (18.0)
Black/African American	70 (5.8)	5 (3.0)	4 (2.5)	7 (4.3)	6 (3.5)	12 (9.1)	13 (9.4)	11 (8.0)	12 (9.4)
White	928 (77.4)	139 (82.2)	124 (77.5)	130 (80.2)	128 (74.9)	94 (71.2)	108 (77.7)	113 (81.9)	92 (71.9)
Other	10 (0.8)	1 (0.6)	1 (0.6)	0	5 (2.9)	0	1 (0.7)	1 (0.7)	1 (0.8)
Ethnic group, n (%)									
Hispanic/Latino	138 (11.5)	18 (10.7)	15 (9.4)	14 (8.6)	24 (14.0)	11 (8.3)	16 (11.5)	21 (15.2)	19 (14.8)
Non-Hispanic/ Latino	1,061 (88.5)	151 (89.3)	145 (90.6)	148 (91.4)	147 (86.0)	121 (91.7)	123 (88.5)	117 (84.8)	109 (85.2)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; HbA_{1c}: glycated haemoglobin; n: number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema: semaglutide.

Supplementary Table 3. Baseline characteristics by diabetes duration subgroups

		≤5 years				>5–10 years				>10 years			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**113**	**128**	**122**	**114**	**101**	**94**	**103**	**92**	**87**	**77**	**75**	**93**
Age, years	56 (10.6)	52.3 (11.0)	51.7 (10.1)	51.1 (11.6)	51.8 (10.2)	55.5 (9.8)	57.0 (8.5)	56.8 (7.9)	57.0 (10.3)	62.3 (9.3)	58.9 (11.0)	60.4 (9.4)	59.9 (9.7)
Sex, n (%)													
Male	662 (55.2)	62 (54.9)	71 (55.5)	61 (50.0)	53 (46.5)	55 (54.5)	46 (48.9)	58 (56.3)	64 (69.6)	52 (59.8)	43 (55.8)	43 (57.3)	54 (58.1)
Female	537 (44.8)	51 (45.1)	57 (44.5)	61 (50.0)	61 (53.5)	46 (45.5)	48 (51.1)	45 (43.7)	28 (30.4)	35 (40.2)	34 (44.2)	32 (42.7)	39 (41.9)
Diabetes duration, years	7.4 (5.7)	2.6 (1.3)	2.5 (1.3)	2.5 (1.4)	2.6 (1.4)	7.0 (1.4)	7.1 (1.3)	7.3 (1.3)	7.0 (1.4)	15.3 (4.9)	14.5 (4.5)	14.9 (5.3)	14.5 (4.4)
HbA_{1c}, %	8.2 (0.9)	8.2 (1.0)	8.1 (0.9)	8.2 (0.9)	8.2 (0.9)	8.3 (1.0)	8.2 (0.9)	8.2 (1.0)	8.2 (0.8)	8.4 (0.9)	8.2 (0.9)	8.2 (0.9)	8.2 (0.9)
HbA_{1c}, mmol/mol	66.4 (10.0)	66.6 (10.8)	65.3 (10.2)	66.6 (9.6)	65.9 (10.1)	67.5 (10.4)	66.1 (9.8)	65.9 (10.5)	66.4 (9.0)	68.6 (10.1)	66.0 (9.8)	65.9 (10.3)	66.2 (10.0)
Body weight, kg	95.2 (22.6)	97.2 (27.6)	96.8 (24.0)	100.4 (23.6)	92.0 (22.9)	95.1 (21.8)	96.6 (23.7)	94.7 (18.1)	95.1 (23.3)	96.8 (23.0)	92.4 (20.3)	88.6 (17.7)	93.5 (18.8)
BMI, kg/m^2	33.5 (6.8)	34.0 (7.9)	34.3 (7.3)	35.1 (7.8)	33.0 (6.7)	33.3 (6.3)	33.9 (7.2)	33.3 (5.4)	33.2 (6.9)	33.7 (7.1)	32.3 (5.7)	31.6 (4.7)	33.1 (6.1)
Race, n (%)													
Asian	191 (15.9)	25 (22.1)	30 (23.4)	19 (15.6)	35 (30.7)	18 (17.8)	11 (11.7)	9 (8.7)	13 (14.1)	7 (8.0)	7 (9.1)	10 (13.3)	7 (7.5)
Black/African American	70 (5.8)	2 (1.8)	8 (6.3)	5 (4.1)	6 (5.3)	6 (5.9)	4 (4.3)	7 (6.8)	1 (1.1)	9 (10.3)	5 (6.5)	6 (8.0)	11 (11.8)
White	928 (77.4)	86 (76.1)	89 (69.5)	97 (79.5)	72 (63.2)	76 (75.2)	79 (84.0)	87 (84.5)	77 (83.7)	71 (81.6)	64 (83.1)	59 (78.7)	71 (76.3)
Other	10 (0.8)	0	1 (0.8)	1 (0.8)	1 (0.9)	1 (1.0)	0	0	1 (1.1)	0	1 (1.3)	0	4 (4.3)

Ethnic group, n (%)													
Hispanic/Latino	138 (11.5)	11 (9.7)	9 (7.0)	13 (10.7)	17 (14.9)	5 (5.0)	7 (7.4)	12 (11.7)	15 (16.3)	13 (14.9)	15 (19.5)	10 (13.3)	11 (11.8)
Non-Hispanic/Latino	1,061 (88.5)	102 (90.3)	119 (93.0)	109 (89.3)	97 (85.1)	96 (95.0)	87 (92.6)	91 (88.3)	77 (83.7)	74 (85.1)	62 (80.5)	65 (86.7)	82 (88.2)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; HbA_{1c}: glycated haemoglobin; n: number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema: semaglutide.

Supplementary Table 4. Baseline characteristics by baseline HbA_{1c} subgroups

		≤7.5% (≤58 mmol/mol)				>7.5–8.5% (>58–69 mmol/mol)				>8.5% (>69 mmol/mol)			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**74**	**94**	**83**	**84**	**120**	**105**	**124**	**120**	**107**	**100**	**93**	**95**
Age, years	56 (10.6)	57.5 (12.2)	57.0 (10.4)	57.7 (11.1)	58.1 (10.2)	57.3 (10.1)	53.3 (10.6)	55.6 (9.7)	55.4 (10.5)	54.3 (10.7)	53.5 (9.9)	53.1 (10.9)	54.5 (10.9)
Sex, n (%)													
Male	662 (55.2)	39 (52.7)	50 (53.2)	48 (57.8)	45 (53.6)	69 (57.5)	53 (50.5)	67 (54.0)	69 (57.5)	61 (57.0)	57 (57.0)	47 (50.5)	57 (60.0)
Female	537 (44.8)	35 (47.3)	44 (46.8)	35 (42.2)	39 (46.4)	51 (42.5)	52 (49.5)	57 (46.0)	51 (42.5)	46 (43.0)	43 (43.0)	46 (49.5)	38 (40.0)
Diabetes duration, years	7.4 (5.7)	6.7 (4.6)	7.0 (6.2)	8.0 (5.9)	8.0 (6.5)	7.8 (6.1)	6.9 (4.8)	6.3 (5.0)	7.4 (5.5)	8.3 (6.5)	7.1 (5.5)	7.9 (6.1)	7.6 (5.0)
HbA_{1c}, %	8.2 (0.9)	7.3 (0.2)	7.2 (0.2)	7.2 (0.2)	7.2 (0.2)	8.0 (0.3)	8.0 (0.3)	8.0 (0.3)	8.0 (0.3)	9.4 (0.6)	9.3 (0.5)	9.4 (0.6)	9.3 (0.5)
HbA_{1c}, mmol/mol	66.4 (10.0)	55.8 (2.4)	55.4 (2.3)	55.6 (2.3)	55.7 (2.3)	64.0 (3.1)	63.5 (2.9)	63.9 (3.0)	64.1 (3.1)	79.4 (6.5)	77.7 (5.8)	78.7 (6.6)	78.0 (5.7)
Body weight, kg	95.2 (22.6)	99.1 (24.1)	96.9 (21.9)	97.9 (24.3)	93.0 (21.5)	97.4 (22.9)	94.8 (23.0)	94.8 (18.9)	93.8 (21.5)	93.4 (26.1)	95.3 (24.2)	94.3 (20.3)	93.3 (22.7)
BMI, kg/m^2	33.5 (6.8)	34.2 (6.9)	34.0 (6.3)	34.6 (8.3)	33.4 (6.7)	34.1 (6.7)	33.4 (7.4)	33.1 (4.9)	33.1 (6.7)	32.8 (7.7)	33.5 (7.0)	33.4 (6.5)	32.8 (6.3)
Race, n (%)													
Asian	191 (15.9)	5 (6.8)	12 (12.8)	12 (14.5)	17 (20.2)	18 (15.0)	15 (14.3)	13 (10.5)	23 (19.2)	27 (25.2)	21 (21.0)	13 (14.0)	15 (15.8)
Black/African American	70 (5.8)	8 (10.8)	6 (6.4)	8 (9.6)	6 (7.1)	5 (4.2)	6 (5.7)	6 (4.8)	9 (7.5)	4 (3.7)	5 (5.0)	4 (4.3)	3 (3.2)
White	928 (77.4)	61 (82.4)	76 (80.9)	63 (75.9)	60 (71.4)	96 (80.0)	84 (80.0)	105 (84.7)	87 (72.5)	76 (71.0)	72 (72.0)	75 (80.6)	73 (76.8)
Other	10 (0.8)	0	0	0	1 (1.2)	1 (0.8)	0	0	1 (0.8)	0	2 (2.0)	1 (1.1)	4 (4.2)

Ethnic group, n (%)													
Hispanic/Latino	138 (11.5)	6 (8.1)	8 (8.5)	8 (9.6)	7 (8.3)	8 (6.7)	8 (7.6)	15 (12.1)	15 (12.5)	15 (14.0)	15 (15.0)	12 (12.9)	21 (22.1)
Non-Hispanic/Latino	1,061 (88.5)	68 (91.9)	86 (91.5)	75 (90.4)	77 (91.7)	112 (93.3)	97 (92.4)	109 (87.9)	105 (87.5)	92 (86.0)	85 (85.0)	81 (87.1)	74 (77.9)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema: semaglutide.

Supplementary Table 5. Subject demographics and baseline characteristics by baseline BMI

		<30 kg/m²				30–<35 kg/m²				≥35 kg/m²			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**99**	**100**	**91**	**109**	**90**	**86**	**105**	**81**	**112**	**113**	**104**	**108**
Age, years	56 (10.6)	57.4 (11.2)	56.0 (11.4)	57.5 (10.4)	56.9 (10.5)	58.7 (10.1)	55.3 (9.6)	54.4 (11.8)	57.9 (10.7)	53.3 (10.7)	54.5 (10.0)	54.6 (9.3)	53.5 (10.4)
Sex, n (%)													
Male	662 (55.2)	57 (57.6)	60 (60.0)	56 (61.5)	71 (65.1)	53 (58.9)	44 (51.2)	62 (59.0)	47 (58.0)	59 (52.7)	56 (49.6)	44 (42.3)	52 (48.1)
Female	537 (44.8)	42 (42.4)	40 (40.0)	35 (38.5)	38 (34.9)	37 (41.1)	42 (48.8)	43 (41.0)	34 (42.0)	53 (47.3)	57 (50.4)	60 (57.7)	56 (51.9)
Diabetes duration, years	7.4 (5.7)	8.0 (6.9)	8.0 (6.3)	9.0 (6.9)	7.3 (5.8)	7.5 (5.1)	6.2 (4.6)	7.0 (4.9)	7.9 (5.7)	7.7 (5.6)	6.7 (5.3)	6.0 (4.8)	7.8 (5.5)
HbA_{1c}, %	8.2 (0.9)	8.4 (1.0)	8.2 (0.9)	8.3 (1.0)	8.1 (0.9)	8.2 (1.0)	8.2 (1.0)	8.1 (0.8)	8.2 (0.8)	8.3 (0.9)	8.1 (0.9)	8.2 (0.9)	8.3 (0.9)
HbA_{1c}, mmol/mol	66.4 (10.0)	68.6 (10.9)	65.7 (9.6)	66.9 (10.8)	65.5 (9.8)	66.2 (10.6)	66.4 (10.8)	65.5 (9.1)	65.9 (8.7)	67.4 (9.9)	65.1 (9.6)	66.3 (10.3)	66.9 (10.3)
Body weight, kg	95.2 (22.6)	73.8 (12.4)	75.1 (12.4)	78.4 (13.0)	74.7 (12.6)	94.1 (12.6)	91.8 (11.6)	92.8 (12.3)	93.5 (11.3)	118.2 (20.1)	116.8 (18.2)	113.2 (19.7)	112.3 (18.5)
BMI, kg/m²	33.5 (6.8)	26.5 (2.5)	26.8 (2.3)	27.2 (2.2)	26.7 (2.5)	32.6 (1.4)	32.3 (1.4)	32.4 (1.5)	32.7 (1.5)	40.9 (5.5)	40.7 (5.1)	40.5 (5.5)	39.8 (4.9)
Race, n (%)													
Asian	191 (15.9)	37 (37.4)	31 (31.0)	23 (25.3)	41 (37.6)	9 (10.0)	14 (16.3)	13 (12.4)	7 (8.6)	4 (3.6)	3 (2.7)	2 (1.9)	6 (5.6)
Black/African American	70 (5.8)	2 (2.0)	7 (7.0)	9 (9.9)	4 (3.7)	5 (5.6)	3 (3.5)	5 (4.8)	6 (7.4)	10 (8.9)	7 (6.2)	4 (3.8)	8 (7.4)
White	928 (77.4)	60 (60.6)	62 (62.0)	59 (64.8)	63 (57.8)	76 (84.4)	69 (80.2)	87 (82.9)	67 (82.7)	97 (86.6)	101 (89.4)	97 (93.3)	90 (83.3)
Other	10 (0.8)	0	0	0	1 (0.9)	0	0	0	1 (1.2)	1 (0.9)	2 (1.8)	1 (1.0)	4 (3.7)

Ethnic group, n (%)													
Hispanic/Latino	138 (11.5)	8 (8.1)	15 (15.0)	13 (14.3)	18 (16.5)	10 (11.1)	7 (8.1)	13 (12.4)	11 (13.6)	11 (9.8)	9 (8.0)	9 (8.7)	14 (13.0)
Non-Hispanic/Latino	1,061 (88.5)	91 (91.9)	85 (85.0)	78 (85.7)	91 (83.5)	80 (88.9)	79 (91.9)	92 (87.6)	70 (86.4)	101 (90.2)	104 (92.0)	95 (91.3)	94 (87.0)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; HbA_{1c}: glycated haemoglobin; n: number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema: semaglutide.

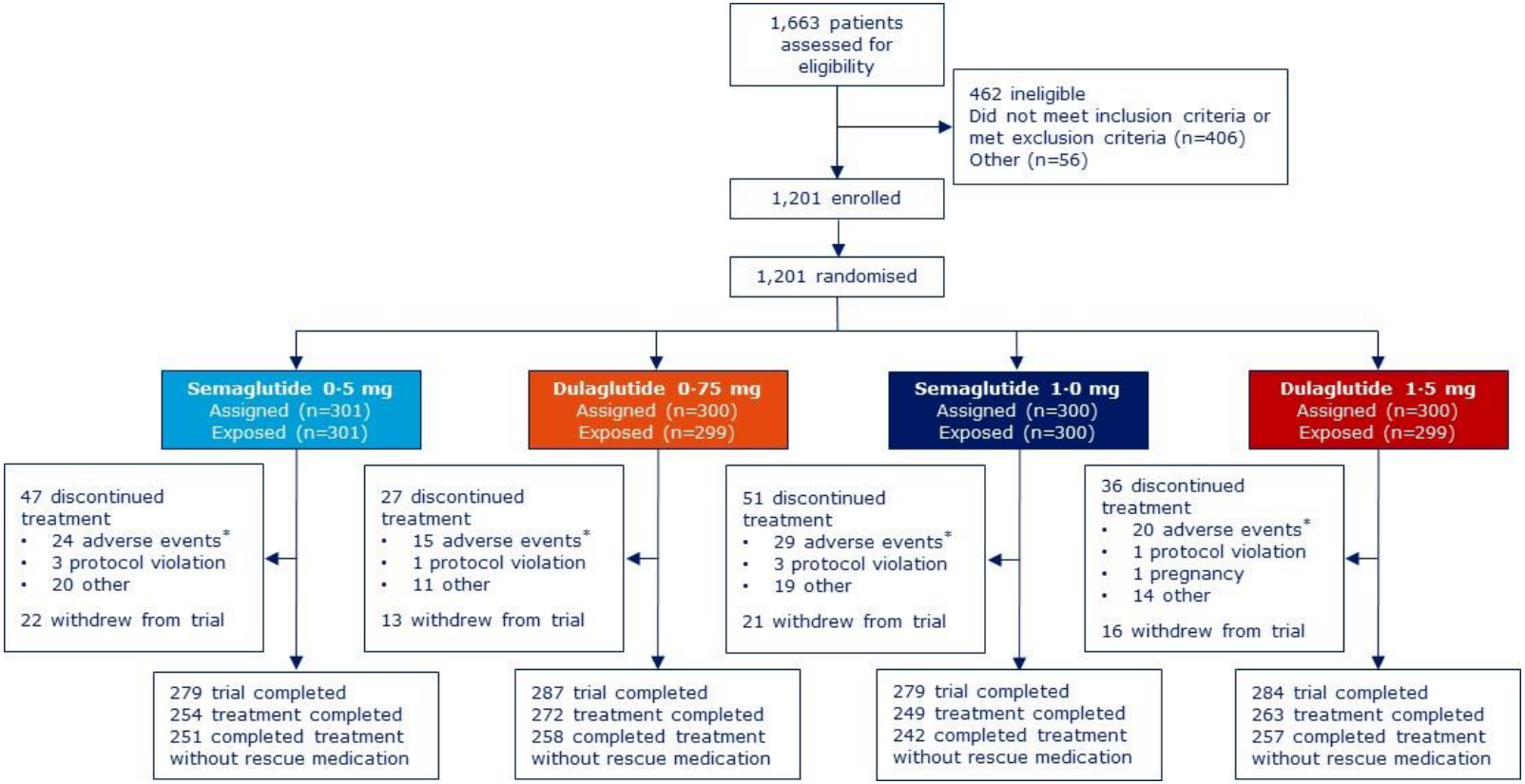
Supplementary Table 6. Baseline characteristics of subjects with BMI <25 kg/m² at baseline

	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**24**	**19**	**16**	**28**
Age, years	56 (10.6)	56.9 (10.0)	51.2 (12.1)	61.8 (11.5)	56.8 (11.8)
Sex, n (%)					
Male	662 (55.2)	15 (62.5)	13 (68.4)	8 (50.0)	18 (64.3)
Female	537 (44.8)	9 (37.5)	6 (31.6)	8 (50.0)	10 (35.7)
Diabetes duration, years	7.4 (5.7)	6.8 (6.4)	7.8 (6.6)	12.2 (9.2)	7.3 (5.7)
HbA_{1c}, %	8.2 (0.9)	8.8 (1.1)	8.5 (0.8)	8.4 (1.1)	8.3 (1.1)
HbA_{1c}, mmol/mol	66.4 (10.0)	72.4 (11.5)	69.6 (8.6)	68.2 (12.1)	67.6 (11.5)
Body weight, kg	95.2 (22.6)	62.9 (8.2)	61.8 (9.7)	64.5 (8.4)	62.4 (7.8)
BMI, kg/m²	33.5 (6.8)	23.0 (1.6)	23.1 (1.6)	23.4 (1.6)	23.1 (1.2)
Race, n (%)					
Asian	191 (15.9)	17 (70.8)	9 (47.4)	7 (43.8)	16 (57.1)
Black/African American	70 (5.8)	0	0	0	1 (3.6)
White	928 (77.4)	7 (29.2)	10 (52.6)	9 (56.3)	11 (39.3)
Other	10 (0.8)	0	0	0	0
Ethnic group, n (%)					
Hispanic/Latino	138 (11.5)	2 (8.3)	5 (26.3)	3 (18.8)	3 (10.7)
Non-Hispanic/Latino	1,061 (88.5)	22 (91.7)	14 (73.7)	13 (81.3)	25 (89.3)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; HbA_{1c}: glycated haemoglobin; n: number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema: semaglutide.

SUPPLEMENTARY SECTION III: SUBJECT DISPOSITION

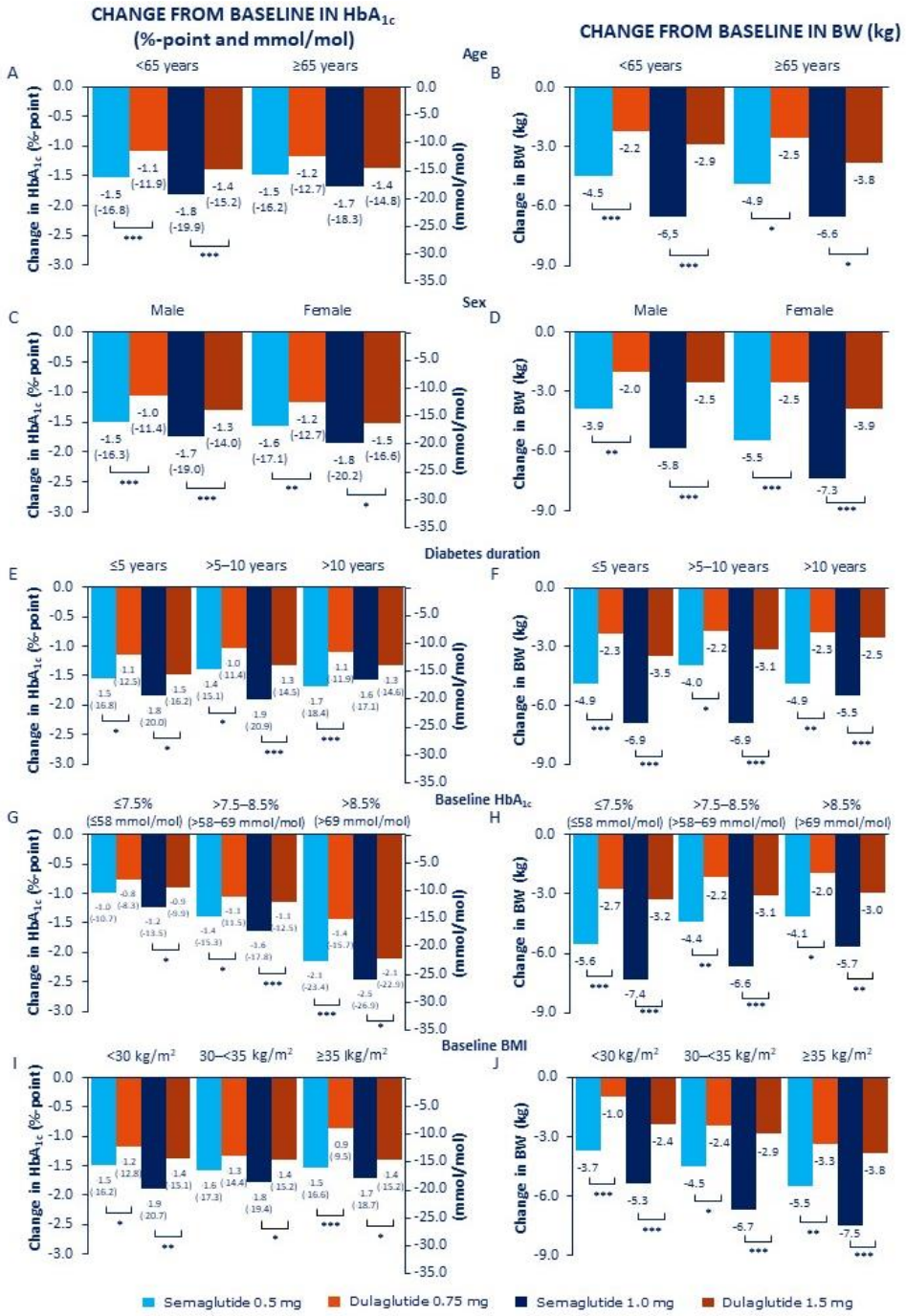
Supplementary Figure 1. Subject disposition in SUSTAIN 7.



*Reflects primary reason for treatment discontinuation, as judged by the investigator. 'Completed trial' refers to those patients who attended the follow-up visit. 'Completed treatment' refers to those patients who did not discontinue treatment prematurely (with or without the addition of rescue medication).

SUPPLEMENTARY SECTION IV: GLYCAEMIC TARGETS & WEIGHT-LOSS RESPONSES

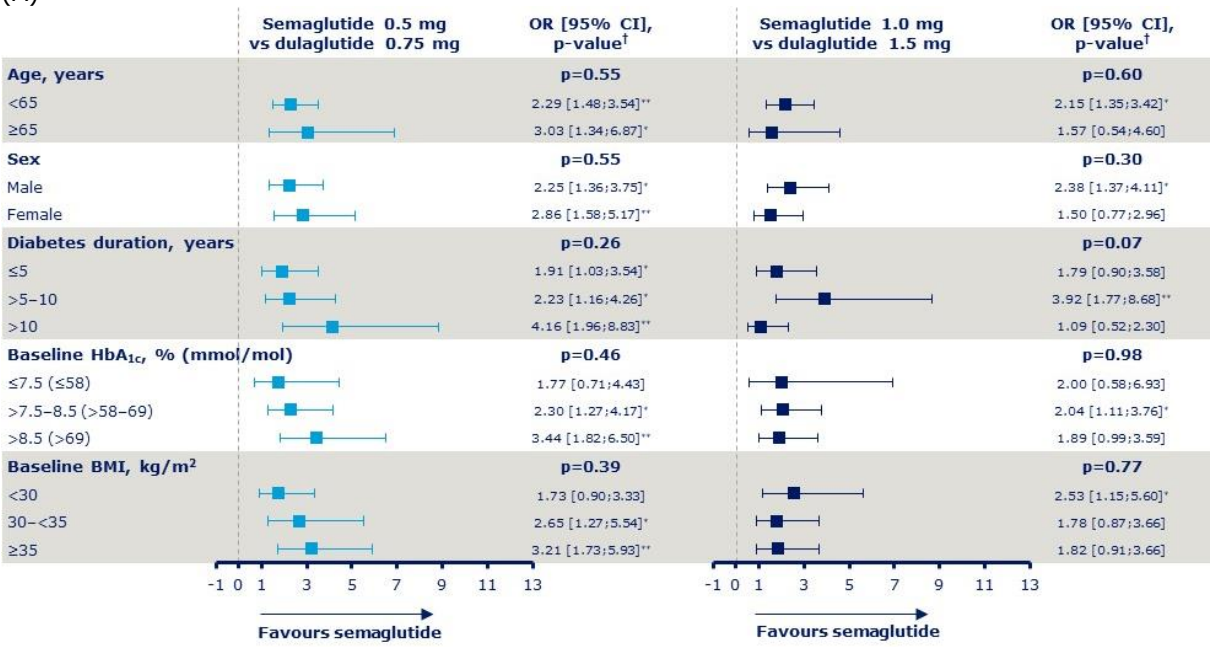
Supplementary Figure 2. Change from baseline in HbA_{1c} (A, C, E, G, I) and body weight (B, D, F, H, J) at week 40 by age (A, B), sex (C, D), diabetes duration (E, F), HbA_{1c} (G, H) and BMI (I, J) at baseline.



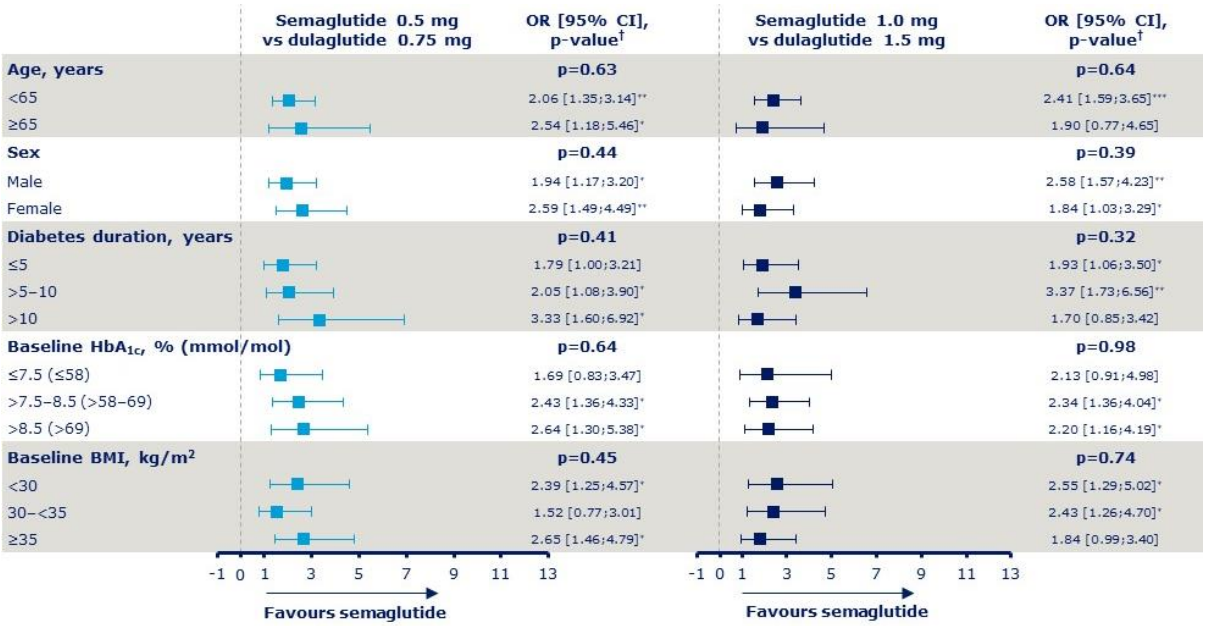
*p<0.05, **p<0.001, ***p<0.0001. Values are estimated means from ANCOVAs controlled for baseline HbA_{1c} (A, C, E, G, I) or BW (B, D, F, H, I) with multiple imputations using data from all randomised subjects exposed to at least one dose of trial product and did not discontinue treatment or receive any non-investigational antihyperglycaemic treatment (full analysis set) obtained while on treatment and prior to onset of rescue medication. P-values are based on ETDs; statistical analyses were not performed for change from baseline. ANCOVA: analysis of covariance; BMI: body mass index; BW: body weight; ETD: estimated treatment difference; HbA_{1c}: glycated haemoglobin.

Supplementary Figure 3. Odds ratios for the proportion of subjects achieving HbA_{1c} <7.0% (53 mmol/mol; A) and HbA_{1c} ≤6.5% (48 mmol/mol; B) at 40 weeks by age, sex, diabetes duration, HbA_{1c} and BMI at baseline

(A)



(B)

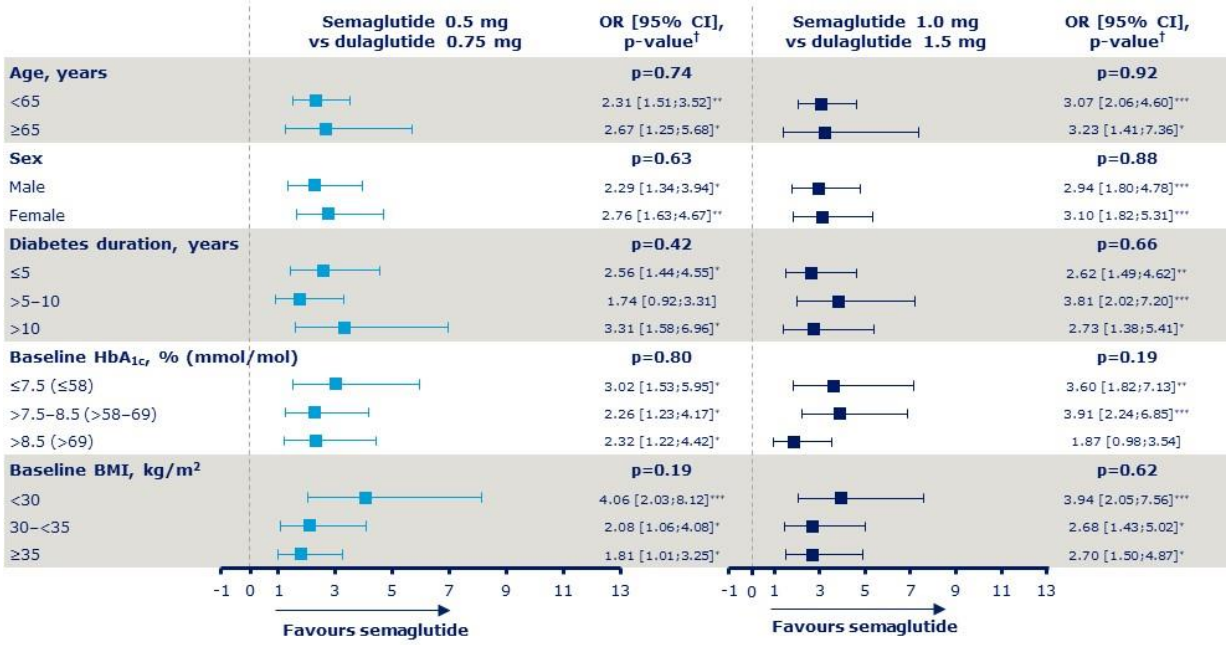


*p<0.05, **p<0.001, ***p<0.0001; †p-values represent the test for treatment by subgroup interaction. Values are ORs [95% CIs] from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data

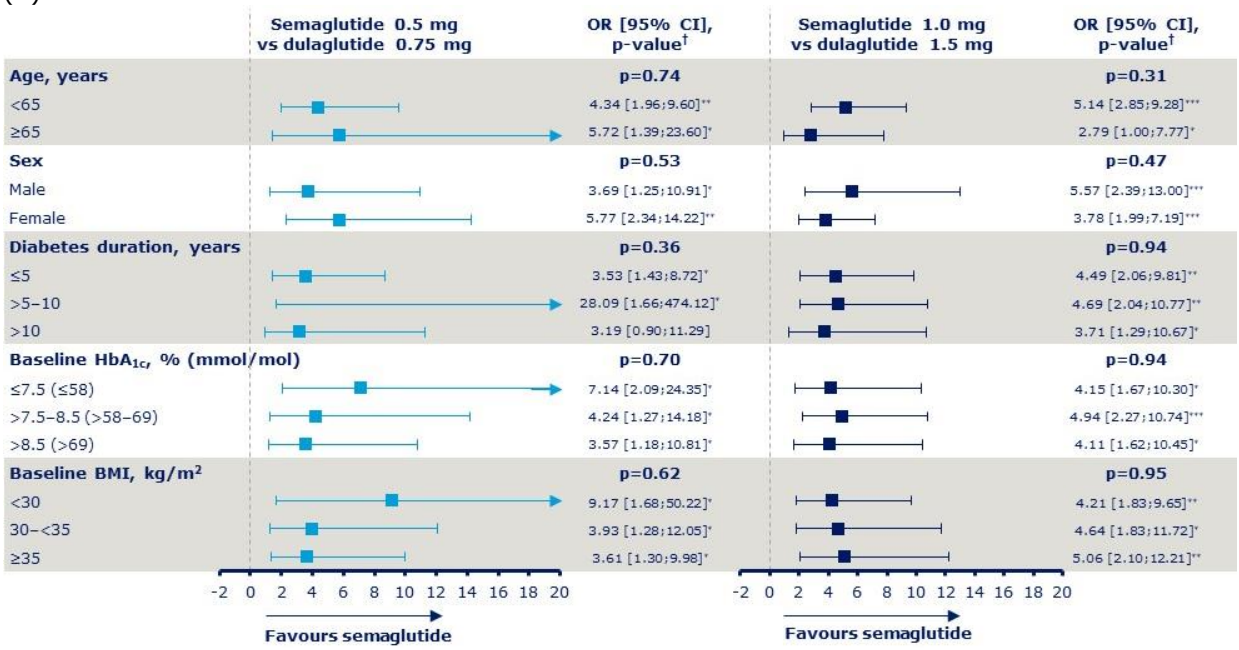
from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA: analysis of covariance; BMI: body mass index; CI: confidence interval; HbA_{1c}: glycated haemoglobin; OR: odds ratio.

Supplementary Figure 4. Odds ratios for the proportion of subjects achieving weight loss ≥5% (A) and weight loss ≥10% (B) at 40 weeks by age, sex, diabetes duration, HbA_{1c} and BMI at baseline

(A)

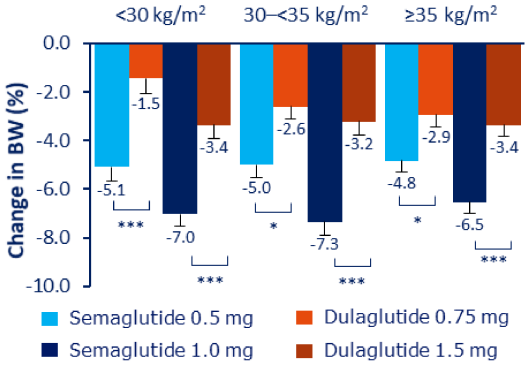


(B)



*p<0.05, **p<0.001, ***p<0.0001; †p-values represent the test for treatment by subgroup interaction. Values are ORs [95% CIs] from ANCOVA analyses with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA: analysis of covariance; BMI: body mass index; CI: confidence interval; HbA_{1c}: glycated haemoglobin; OR: odds ratio.

Supplementary Figure 5: Change in body weight (%) from baseline to week 40 by baseline BMI category



*p<0.05, ***p<0.0001. Values are estimated means from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA: analysis of covariance; BMI: body mass index; BW: body weight.

Supplementary Section V: Adverse Events

Supplementary Table 7. Adverse events by sex subgroups

n (%)	All subjects	Male				Female			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	**169**	**160**	**162**	**171**	**132**	**139**	**138**	**128**
AEs	818 (68.2)	111 (65.7)	97 (60.6)	113 (69.8)	129 (75.4)	93 (70.5)	89 (64.0)	94 (68.1)	92 (71.9)
Serious AEs	86 (7.2)	11 (6.5)	15 (9.4)	10 (6.2)	12 (7.0)	6 (4.5)	9 (6.5)	13 (9.4)	10 (7.8)
AEs leading to premature treatment discontinuation	87 (7.3)	13 (7.7)	8 (5.0)	15 (9.3)	12 (7.0)	11 (8. 3)	6 (4.3)	14 (10.1)	8 (6.3)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	8 (4.7)	1 (0.6)	9 (5.6)	8 (4.7)	8 (6.1)	5 (3.6)	9 (6.5)	6 (4.8)
Gastrointestinal AEs	505 (42.1)	67 (39.6)	47 (29.4)	67 (41.4)	81 (47.4)	62 (47.0)	53 (38.1)	66 (47.8)	62 (48.4)
Vomiting	103 (8.6)	13 (7.7)	5 (3.1)	11 (6.8)	16 (9.4)	18 (13.6)	7 (5.0)	20 (14.5)	13 (10.2)
Nausea	230 (19.2)	29 (17.2)	13 (8.1)	25 (15.4)	33 (19.3)	39 (29.5)	26 (18.7)	38 (27.5)	27 (21.1)
Diarrhoea	160 (13.3)	21 (12.4)	10 (6.3)	19 (11.7)	33 (19.3)	22 (16.7)	13 (9.4)	22 (15.9)	20 (15.6)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	1 (0.6)	3 (1.9)	3 (1.9)	3 (1.8)	1 (0.8)	0	2 (1.4)	2 (1.6)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event; BG: blood glucose; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema: semaglutide.

Supplementary Table 8. Adverse events by diabetes duration subgroups

n (%)	All subjects	≤5 years				>5–10 years				>10 years			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	**113**	**128**	**122**	**114**	**101**	**94**	**103**	**92**	**87**	**77**	**75**	**93**
AEs	818 (68.2)	76 (67.3)	81 (63.3)	79 (64.8)	76 (66.7)	66 (65.3)	52 (55.3)	74 (71.8)	73 (79.3)	62 (71.3)	53 (68.8)	54 (72.0)	72 (77.4)
Serious AEs	86 (7.2)	5 (4.4)	9 (7.0)	10 (8.2)	9 (7.9)	4 (4.0)	6 (6.4)	7 (6.8)	6 (6.5)	8 (9.2)	9 (11.7)	6 (8.0)	7 (7.5)
AEs leading to premature treatment discontinuation	87 (7.3)	9 (8.0)	3 (2.3)	9 (7.4)	5 (4.4)	10 (9.9)	5 (5.3)	9 (8.7)	8 (8.7)	5 (5.7)	6 (7.8)	11 (14.7)	7 (7.5)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	7 (6.2)	1 (0.8)	6 (4.9)	3 (2.6)	6 (5.9)	1 (1.1)	5 (4.9)	5 (5.4)	3 (3.4)	4 (5.2)	7 (9.3)	6 (6.5)
Gastrointestinal AEs	505 (42.1)	52 (46.0)	44 (34.4)	57 (46.7)	52 (45.6)	44 (43.6)	26 (27.7)	42 (40.8)	48 (52.2)	33 (37.9)	30 (39.0)	34 (45.3)	43 (46.2)
Vomiting	103 (8.6)	14 (12.4)	5 (3.9)	18 (14.8)	8 (7.0)	10 (9.9)	4 (4.3)	6 (5.8)	9 (9.8)	7 (8.0)	3 (3.9)	7 (9.3)	12 (12.9)
Nausea	230 (19.2)	25 (22.1)	17 (13.3)	24 (19.7)	21 (18.4)	22 (21.8)	10 (10.6)	24 (23.3)	20 (21.7)	21 (24.1)	12 (15.6)	15 (20.0)	19 (20.4)
Diarrhoea	160 (13.3)	16 (14.2)	14 (10.9)	22 (18.0)	20 (17.5)	18 (17.8)	4 (4.3)	11 (10.7)	18 (19.6)	9 (10.3)	5 (6.5)	8 (10.7)	15 (16.1)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (0.8)	2 (1.6)	2 (1.8)	0	0	2 (1.9)	2 (2.2)	2 (2.3)	2 (2.6)	1 (1.3)	1 (1.1)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event; BG: blood glucose; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema: semaglutide.

Supplementary Table 9. Adverse events by baseline HbA_{1c} subgroups

n (%)	All subjects	≤7.5% (≤58 mmol/mol)				>7.5–8.5% (>58–69 mmol/mol)				>8.5% (>69 mmol/mol)			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	**74**	**94**	**83**	**84**	**120**	**105**	**124**	**120**	**107**	**100**	**93**	**95**
AEs	818 (68.2)	51 (68.9)	62 (66.0)	57 (68.7)	66 (78.6)	80 (66.7)	65 (61.9)	83 (66.9)	94 (78.3)	73 (68.2)	59 (59.0)	67 (72.0)	61 (64.2)
Serious AEs	86 (7.2)	3 (4.1)	9 (9.6)	6 (7.2)	3 (3.6)	7 (5.8)	8 (7.6)	9 (7.3)	7 (5.8)	7 (6.5)	7 (7.0)	8 (8.6)	12 (12.6)
AEs leading to premature treatment discontinuation	88 (7.3)	6 (8.1)	5 (5.3)	8 (9.6)	11 (13.1)	11 (9.2)	5 (4.8)	12 (9.7)	4 (3.3)	7 (6.5)	4 (4.0)	9 (9.7)	5 (5.3)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	5 (6.8)	2 (2.1)	6 (7.2)	9 (10.7)	6 (5.0)	2 (1.9)	8 (6.5)	1 (0.8)	5 (4.7)	2 (2.0)	4 (4.3)	4 (4.2)
Gastrointestinal AEs	505 (42.1)	33 (44.6)	32 (34.0)	38 (45.8)	50 (59.5)	52 (43.3)	40 (38.1)	53 (42.7)	55 (45.8)	44 (41.1)	28 (28.0)	42 (45.2)	38 (40.0)
Vomiting	103 (8.6)	7 (9.5)	5 (5.3)	8 (9.6)	7 (8.3)	14 (11.7)	2 (1.9)	14 (11.3)	11 (9.2)	10 (9.3)	5 (5.0)	9 (9.7)	11 (11.6)
Nausea	230 (19.2)	16 (21.6)	11 (11.7)	16 (19.3)	19 (22.6)	28 (23.3)	14 (13.3)	28 (22.6)	22 (18.3)	24 (22.4)	14 (14.0)	19 (20.4)	19 (20.0)
Diarrhoea	160 (13.3)	12 (16.2)	6 (6.4)	14 (16.9)	25 (29.8)	20 (16.7)	11 (10.5)	17 (13.7)	17 (14.2)	11 (10.3)	6 (6.0)	10 (10.8)	11 (11.6)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (1.1)	2 (2.4)	1 (1.2)	2 (1.7)	1 (1.0)	1 (0.8)	2 (1.7)	0	1 (1.0)	2 (2.2)	2 (2.1)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event; BG: blood glucose; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema: semaglutide.

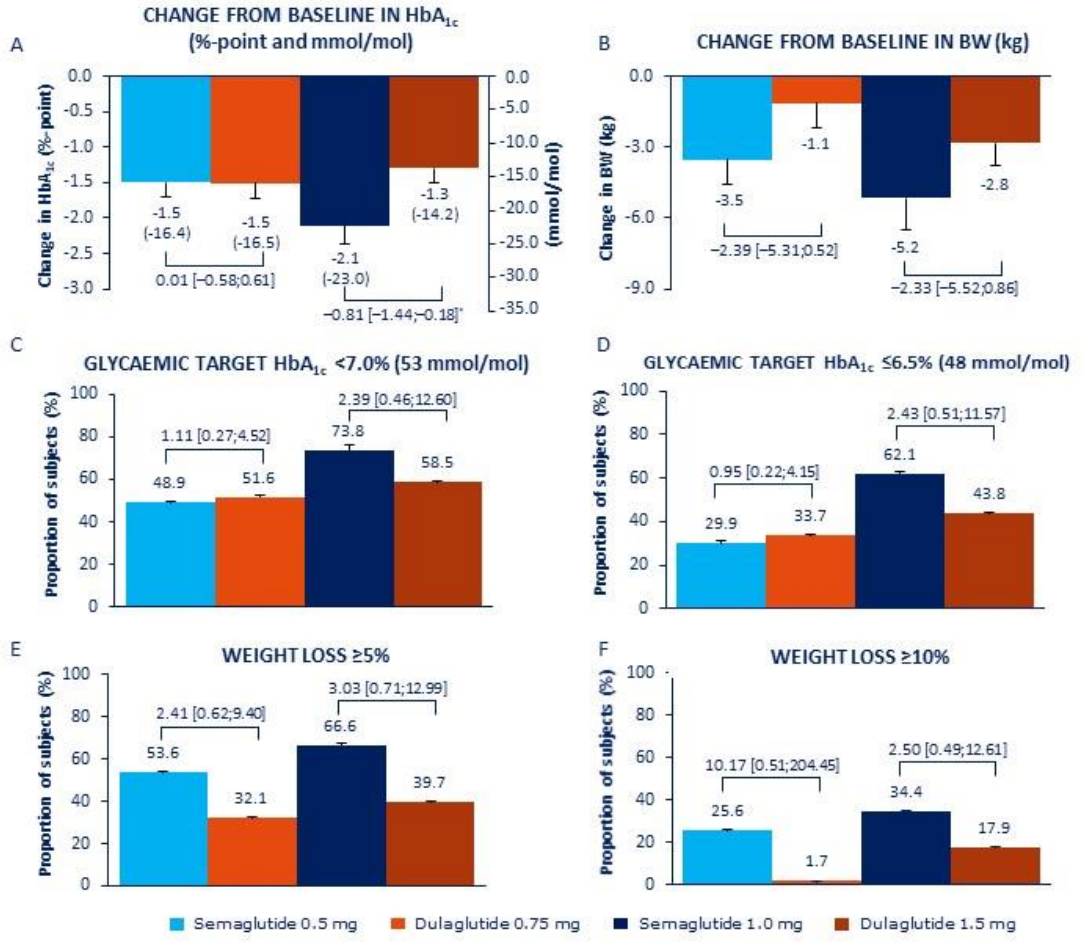
Supplementary Table 10. Adverse events by baseline BMI

n (%)		<30 kg/m^2				30–<35 kg/m^2				≥35 kg/m^2			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	99	100	91	109	90	86	105	81	112	113	104	108
AEs	818 (68.2)	65 (65.7)	60 (60.0)	65 (71.4)	84 (77.1)	60 (66.7)	54 (62.8)	66 (62.9)	65 (80.2)	79 (70.5)	72 (63.7)	76 (73.1)	71 (65.7)
Serious AEs	86 (7.2)	4 (4.0)	4 (4.0)	5 (5.5)	4 (3.7)	6 (6.7)	6 (7.0)	5 (4.8)	12 (14.8)	7 (6.3)	14 (12.4)	13 (12.5)	6 (5.6)
AEs leading to premature treatment discontinuation	87 (7.3)	12 (12.1)	8 (8.0)	12 (13.2)	16 (14.7)	8 (8.9)	5 (5.8)	8 (7.6)	2 (2.5)	4 (3.6)	1 (0.9)	9 (8.7)	2 (1.9)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	9 (9.1)	4 (4.0)	9 (9.9)	11 (10.1)	5 (5.6)	2 (2.3)	5 (4.8)	2 (2.5)	2 (1.8)	0	4 (3.8)	1 (0.9)
Gastrointestinal AEs	505 (42.1)	48 (48.5)	32 (32.0)	44 (48.4)	59 (54.1)	39 (43.3)	27 (31.4)	44 (41.9)	41 (50.6)	42 (37.5)	41 (36.3)	45 (43.3)	42 (38.9)
Vomiting	103 (8.6)	16 (16.2)	5 (5.0)	11 (12.1)	15 (13.8)	6 (6.7)	3 (3.5)	12 (11.4)	4 (4.9)	9 (8.0)	4 (3.5)	8 (7.7)	10 (9.3)
Nausea	230 (19.2)	25 (25.3)	9 (9.0)	19 (20.9)	24 (22.0)	21 (23.3)	11 (12.8)	24 (22.9)	19 (23.5)	22 (19.6)	19 (16.8)	20 (19.2)	17 (15.7)
Diarrhoea	160 (13.3)	18 (18.2)	6 (6.0)	14 (15.4)	28 (25.7)	13 (14.4)	9 (10.5)	14 (13.3)	14 (17.3)	12 (10.7)	8 (7.1)	13 (12.5)	10 (9.3)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (1.0)	0	3 (2.8)	0	1 (1.2)	2 (1.9)	0	2 (1.8)	1 (0.9)	3 (2.9)	2 (1.9)

Data are presented as number and proportion (%) in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event; BG: blood glucose; BMI: body mass index; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema: semaglutide.

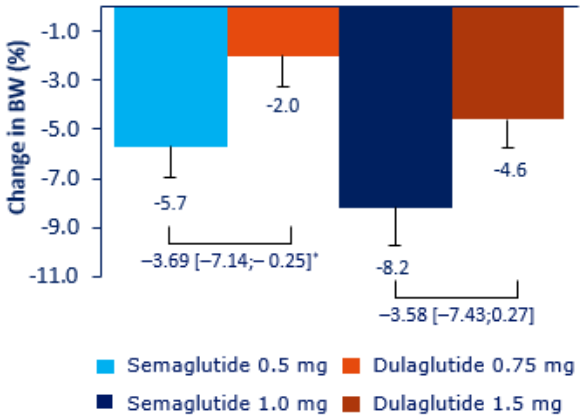
Supplementary Section VI: Results in subjects with BMI <25 kg/m^2

Supplementary Figure 6. Change in HbA_{1c} (A) and body weight (B) from baseline to week 40 and the proportion of subjects achieving HbA_{1c} <7.0% (53 mmol/mol; C), HbA_{1c} ≤6.5% (48 mmol/mol; D), weight loss ≥5% (E) and weight loss ≥10% (F) in subjects with BMI <25 kg/m² at baseline



*p<0.05. Values are estimated means (A, B), estimated proportions (C–F), ETDs [95% CIs] (A, B) or ORs [95% CIs] (C–F) from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set). ANCOVA analyses were controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA: analysis of covariance; BMI: body mass index, BW: body weight; CI: confidence interval; ETD: estimated treatment difference; HbA_{1c}: glycated haemoglobin; OR: odds ratio.

Supplementary Figure 7. Change in body weight (%) from baseline to week 40 in subjects with BMI <25 kg/m^2 at baseline



*p<0.05. Values are estimated means from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set). ANCOVAs were controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA: analysis of covariance; BMI: body mass index; BW: body weight; CI: confidence interval; ETD: estimated treatment difference.

Supplementary Table 11. Adverse events in subjects with BMI <25 kg/m² at baseline

n (%)	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	**24**	**19**	**16**	**28**
AEs	818 (68.2)	18 (75.0)	14 (73.7)	12 (75.0)	23 (82.1)
Serious AEs	86 (7.2)	1 (4.2)	1 (5.3)	2 (12.5)	2 (7.1)
AEs leading to premature treatment discontinuation	87 (7.3)	5 (20.8)	2 (10.5)	4 (25.0)	6 (21.4)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	4 (16.7)	0	2 (12.5)	2 (7.1)
Gastrointestinal AEs	505 (42.1)	14 (58.3)	6 (31.6)	10 (62.5)	17 (60.7)
Vomiting	103 (8.6)	6 (25.0)	1 (5.3)	2 (12.5)	3 (10.7)
Nausea	230 (19.2)	6 (25.0)	1 (5.3)	4 (25.0)	6 (21.4)
Diarrhoea	160 (13.3)	5 (20.8)	3 (15.8)	3 (18.8)	7 (25.0)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (5.3)	0	1 (3.6)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event; BG: blood glucose; BMI: body mass index; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema: semaglutide.

SUPPLEMENTARY SECTION VII: TRIAL PROTOCOL

This supplement contains the following items;

1. Original protocol, final protocol, summary of changes
2. Final statistical analysis plan (one version no further amendments made)

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Protocol

Trial ID: NN9535-4216

Efficacy and safety of semaglutide versus dulaglutide as add-on to metformin in subjects with type 2 diabetes

Trial phase: 3b

Redacted protocol
Includes redaction of personal identifiable information only.

Protocol originator
[redacted], [redacted]
Clinical Operations, Semaglutide

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List of abbreviations

ADA	American Diabetes Association
AACE	American Association of Clinical Endocrinologists
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under curve
BG	blood glucose
BMI	body mass index
CABG	coronary artery bypass graft surgery
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLAE	clinical laboratory adverse event
C_{max}	maximum concentration
CRF	case report form
CT	computerised axial tomography
DFU	direction for use
DPP-4	ubiquitous dipeptidyl peptidase
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit
FPG	fasting plasma glucose
GCP	Good Clinical Practice

GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin
HDL	high density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgE	immunoglobulin E
IND	Investigational New Drug Application
IRB	institutional review board
IWRS	interactive web response system
i.v.	intravenous
LC-MS/MS	liquid chromatography coupled with tandem mass spectrometry
LDL	low density lipoprotein
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LPFV	last patient first visit
LPLV	last patient last visit
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MESI	medical event of special interest
MI	myocardial infarction
MMRM	model for repeated measures
MRI	magnetic resonance imaging
NA or N/A	not applicable
ND	not done
NOAEL	no observable adverse effect level
NYHA	New York Heart Association
OAD	oral antidiabetic drug
P	phone contact
PCI	percutaneous coronary intervention
PG	plasma glucose

PP	per protocol
PRO	patient reported outcome
QALY	quality adjusted life years
RA	receptor agonist
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous(ly)
SF-36v2™	short form health survey
SMPG	self-measured plasma glucose
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
T2D	type 2 diabetes
TEAE	treatment emergent adverse event
TIA	transient ischaemic attack
t_{max}	time to maximum concentration
TSH	thyroid-stimulating hormone
UNL	upper normal limit
UNR	upper normal range
UTN	Universal Trial Number
V	visit

1 Summary

Objective(s) and endpoint(s):

Primary objective

To compare the effect of once-weekly dosing of two dose levels of subcutaneous semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of two dose levels of subcutaneous dulaglutide (0.75 mg and 1.5 mg) on glycaemic control in subjects with type 2 diabetes on a background treatment with metformin.

Primary endpoint

Change from baseline to week 40 in HbA_{1c}

Key secondary objective

To compare the effect of once-weekly dosing of two dose levels of subcutaneous semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of two dose levels of subcutaneous dulaglutide (0.75 mg and 1.5 mg) in subjects with type 2 diabetes on a background treatment with metformin with regards to:

- Body weight control
- Blood pressure
- Patient reported outcomes
- Safety and tolerability

Key secondary endpoints

- Change from baseline to week 40 in body weight (kg)

Change from baseline to week 40 in:

- Fasting plasma glucose
- Systolic and diastolic blood pressure
- Overall scores for patient reported outcomes: Diabetes Treatment Satisfaction Questionnaire

Subjects who after 40 weeks treatment achieve (yes/no):

- HbA_{1c} ≤6.5% (48 mmol/mol) American Association of Clinical Endocrinologists target

Trial design:

The trial is a 40-week randomised, open-label, active-controlled, parallel group, multicentre, multinational, four-armed trial.

Subjects with type 2 diabetes inadequately controlled with metformin alone will after approximately 2 weeks screening period be randomised in a 1:1:1:1 manner to receive either a dose of 0.5 mg or 1.0 mg of semaglutide once-weekly or 0.75 mg or 1.5 mg of dulaglutide once-weekly.

After the treatment period of approximately 40 weeks in total, all subjects enter a follow-up period of 5 weeks ended by a follow-up phone contact. Total trial duration for the individual subjects will be approximately 47 weeks.

Trial population:

A planned total number of 1196 subjects will be randomised.

Key inclusion criteria

- Male or female, age ≥ 18 years at the time of signing informed consent.
- HbA_{1c} 7.0 – 10.5% (53 – 91 mmol/mol) (both inclusive)
- Subjects on stable diabetes treatment with metformin (minimum of 1500 mg/day or maximal tolerated dose documented in the patient medical record) for 90 days prior to screening

Key exclusion criteria

- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).
- Any condition, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol
- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening. An exception is short-term insulin treatment for acute illness for a total of ≤14 days
- History of pancreatitis (acute or chronic)
- Screening calcitonin ≥50 ng/L
- Family or personal history of Multiple Endocrine Neoplasia Type 2 or Medullary Thyroid Carcinoma
- Renal impairment defined as eGFR < 60 mL/min/1.73 m^2 as per CKD-EPI
- Subjects presently classified as being in New York Heart Association Class IV
- Planned coronary, carotid or peripheral artery revascularisation on the day of screening
- Proliferative retinopathy or maculopathy requiring acute treatment
- History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas)
- Anticipated initiation or change in concomitant medications (for more than 14 consecutive days or on a frequent basis) known to affect weight or glucose metabolism (e.g. orlistat, thyroid hormones, corticosteroids)

Assessments:

- Glucose metabolism (HbA_{1c}, fasting plasma glucose)
- Body measurements (weight (in kg), body mass index (BMI) and waist circumference)
- Blood pressure (sitting)
- Fasting blood lipids (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides)
- Self-measured plasma glucose (7-point profile)
- Patient reported outcomes
- Adverse events and serious adverse events
- Hypoglycaemic episodes
- Biochemistry and haematology
- Pulse
- Calcitonin
- Physical examination
- Electrocardiogram

Trial product(s):

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

- Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Dulaglutide, solution for injection, 0.75 mg/0.5 mL in a pre-filled pen
- Dulaglutide, solution for injection, 1.5 mg/0.5 mL in a pre-filled pen

2 Flow chart

Trial Periods	Screening	Randomisation	Treatment						End of treatment[1] (EOT)	Follow-up[1]	EOT Premature discontinuation[2]	Follow-up Premature discontinuation[2]
Visit (V)/ phone contact (P)	V1	V2	V3	P4	V5	V6	V7	V8	V9	P10	V9A	P10A
Timing of visit (weeks)	-2	0	4	6	8	12	16	28	40	45		
Visit window (days)	±7		±3	±3	±3	±3	±3	±3	±7	+7		
SUBJECT RELATED INFO/ASSESSMENTS												
Informed consent	X											
In/exclusion criteria	X	X										
Randomisation		X										
Concomitant illness	X											
Medical history	X											
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X											
Diagnosis of diabetes	X											
Tobacco use	X											
History of cardiovascular disease	X											
History of gallbladder disease	X											
Withdrawal criteria			X	X	X	X	X	X	X		X	
EFFICACY												
Height		X										
Body weight		X	X		X	X	X	X	X		X	
BMI		X	X		X	X	X	X	X		X	
Waist circumference		X					X		X		X	
Blood pressure, sitting	X	X	X		X	X	X	X	X		X	
Fasting plasma glucose		X	X		X	X	X	X	X		X	
HbA_{1c}	X	X	X		X	X	X	X	X		X	
Lipids		X					X		X		X	
7-point profile		X					X		X		X	

Trial Periods	Screening	Randomisation	Treatment						End of treatment[1] (EOT)	Follow-up[1]	EOT Premature discontinuation[2]	Follow-up Premature discontinuation[2]
Visit (V)/ phone contact (P)	V1	V2	V3	P4	V5	V6	V7	V8	V9	P10	V9A	P10A
Timing of visit (weeks)	-2	0	4	6	8	12	16	28	40	45		
Visit window (days)	±7		±3	±3	±3	±3	±3	±3	±7	+7		
PRO questionnaires		X					X		X		X	
SAFETY												
Adverse events		X[3]	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	X	X	X	X	X	X	X	X	X	X	X	X
ECG[4]		X					X		X		X	
Fundoscopy/Fundus photography[5]		X										
Physical examination	X						X		X		X	
Pulse, sitting	X	X	X		X	X	X	X	X		X	
Biochemistry		X	X		X		X	X	X		X	
Creatinine (including eGFR)	X	X	X		X		X	X	X		X	
Haematology		X	X		X		X	X	X		X	
Pregnancy test[6]	X	X							X		X	
Calcitonin	X						X		X		X	
TRIAL MATERIAL												
Dispensing visit		X			X		X	X				
Drug accountability					X		X	X	X		X	
IWRS call	X	X			X		X	X	X		X	
REMINDERS												
End of trial										X		
Attend visit fasting[7]		X	X		X	X	X	X	X		X	
Direction for use (DFU)		X										
Dispense diary	X	X	X		X	X	X	X	X		X	
Collect and review diary[8]		X	X		X	X	X	X	X		X	
Dispense blood glucose meter	X											
Hand out subject ID card	X											
Training in pen handling		X	X									

Footer	Description
x[1]	V9 (End of treatment) and P10 (Follow-up) are applicable for all randomised subjects, except for subjects who are withdrawn. Subjects who have discontinued trial product prematurely should also attend V9 and P10 according to their initially scheduled week 40 and week 45 visits.
x[2]	Subjects discontinuing trial product prematurely will be asked to attend two additional visits to undergo assessments: End of treatment - premature discontinuation (V9A) and Follow-up - premature discontinuation (P10A). V9A should be scheduled as soon as possible after discontinuation of the trial product. P10A should be scheduled 5 weeks after discontinuation of trial product (+7 days visit window). If a subject withdraws from the trial, the investigator must aim to undertake procedures similar to those for V9A as soon as possible after discontinuation of trial product and P10A should be scheduled 5 weeks after the subject has discontinued trial product (+7 days window). If a subject has already prematurely discontinued from trial product and previously attended visit 9A (end of treatment) and follow-up phone contact (10A), no further visits should be attended.
x[3]	Includes AEs from the first trial-related activity after the subject has signed the informed consent at V1. Procedures and assessments performed at visit 1 and/or 2 are considered screening procedures. The result of these procedures should be considered pre-existing conditions and should be reported as medical history or concomitant illness.
x[4]	ECG performed within 7 days prior to the screening visit is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime.
x[5]	Fundoscopy/fundus photography performed within 90 days before visit 2 is acceptable if results are available for evaluation at the visit 2 and no deterioration in visual function since last assessment.
x[6]	For women of child bearing potential: For site visits 1, 9 and 9A a serum pregnancy test must be performed. At the randomisation visit, a urine pregnancy test must be performed prior to randomisation. In case a menstrual period is missed or if pregnancy is suspected at any time during the trial, a urine pregnancy test should be performed. The subject should be instructed not to dose trial product before pregnancy has been ruled out.
x[7]	Fasting is defined as having consumed only water within the last 6 hours prior to visit. Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed but other prescribed medication should be taken as prescribed.
x[8]	If any hypoglycaemic events are reported at P10 or P10A, information related to hypoglycaemic event(s) should be documented in the subject's medical record and the entry in the medical record will be considered source data.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP)[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki.[2]

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

3.1 Background information

3.1.1 Type 2 diabetes

Type 2 diabetes (T2D) is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver.[3]

Optimal glycaemic control is the treatment goal in subjects with T2D in order to prevent long-term complications associated with chronic hyperglycaemia.[4] Despite the availability of several antidiabetic drugs and insulin, a significant proportion of subjects with T2D do not achieve the recommended blood glucose (BG) target levels.[5,6]

3.1.2 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the L-cells in the small intestine. An incretin hormone is a gut-derived peptide with important physiological function in augmenting postprandial insulin secretion in response to ingestion of a meal. GLP-1 has a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets (i.e. when plasma glucose (PG) levels are above normal).[7,8] Both these effects are considered of importance for the glucose lowering effect of GLP-1.[9] Physiologically, GLP-1 has a pronounced inhibitory effect on gastric emptying.[10] This effect seems to diminish upon chronic exposure to GLP-1.[11,12] At supra-physiological levels GLP-1 also lowers body weight due to a decreased energy intake induced by a lowered appetite.[13]

Subjects with diabetes have a decreased incretin effect.[14-17] However, the insulinotropic action of GLP-1 and thus, the ability to lower BG is preserved in subjects with T2D when administered at supra-physiological levels.[18]

The mechanism of action makes GLP-1 a potent BG lowering agent[19] and thus an attractive pharmacological tool for treatment of T2D.[10,20,21] However, the very short elimination half-life ($t_{½}$) of endogenous GLP-1, $t_{½}$ <1.5 minutes after intravenous (i.v.) administration, due to rapid

degradation by ubiquitous dipeptidyl peptidase (DPP-4)[22] makes native GLP-1 an unattractive treatment option. Clinical trials have revealed that 24-hour infusion of native GLP-1 would be necessary to achieve satisfactory glycaemic control.[23] Therefore, to benefit from the potentials of GLP-1 in treatment of diabetes it has been necessary to develop GLP-1 receptor agonists (RA) with longer half-lives.

3.1.3 Semaglutide

Semaglutide is a potent human GLP-1 analogue for subcutaneous (s.c.) administration. It is structurally similar to liraglutide (Victoza®), a once-daily GLP-1 analogue developed by Novo Nordisk and approved worldwide for the treatment of T2D.

For the semaglutide molecule the principal mechanism of protraction is albumin binding facilitated by a large fatty acid derived chemical moiety attached to the lysine in position 26. The specific modifications in the molecule are: 1) a modification in position 8 (alanine to 2-aminoisobutyric acid) of the peptide backbone in order to further increase stability against DPP-4, and a change in position 34 from a lysine to an arginine in order to only have one (1) lysine in the sequence; 2) a large hydrophilic linker between the lysine in position 26 and the gamma glutamate whereto the fatty acid is attached; 3) a C18 fatty di-acid with a terminal acidic group. The latter two (2) contribute to increased albumin binding which results in decreased renal clearance. In addition to slowed degradation in plasma and decreased renal clearance, delayed absorption from subcutis possibly also contributes to a prolonged half-life $t_{½}$ of 155-183 hours.

In vitro receptor studies have shown that semaglutide is a potent and selective GLP-1 analogue, and animal studies using non-diabetic rats, non-diabetic pigs and diabetic mice have shown lowering of BG and inhibition of food intake. A clinically relevant effect on glucose metabolism and body weight has also been observed in humans.

3.1.4 Nonclinical data - semaglutide

The nonclinical programme for semaglutide was designed according to the ICH M3[24] guideline to support the clinical development. The standard nonclinical data package required to support phase 3 clinical trials has been completed. In addition, 2-year carcinogenicity studies and a pre- and postnatal development toxicity study have been completed.

Semaglutide is generally well tolerated with expected GLP-1 effects on food intake and body weight being dose limiting in mice, rats and cynomolgus monkeys. Two potential safety issues have been identified.

3.1.4.1 Thyroid C-cell tumours in rodents

Treatment-related non-genotoxic proliferative changes in the thyroid C-cells of mice and rats were observed in 2-year carcinogenicity studies with semaglutide. Early C-cell changes were also

identified in repeated dose toxicity studies with semaglutide in mice. However, this was not the case in other species including a 52-week repeat dose study in non-human primates at exposure levels up to 36-fold above the expected clinical exposure. The observed pattern of effects in mice and rats (thyroid C-cell proliferation preceded by increase in serum calcitonin) and lack of these effects in the non-human primate and in man suggest that the mechanism by which semaglutide acts on the thyroid C-cells in rodents is the same as has been demonstrated for other GLP-1 RAs, including liraglutide. The relevance for human subjects is unknown. Recently published data have shown that the GLP-1 receptor is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor mediated C-cell changes in humans is considered to be low.[25]

3.1.4.2 Teratogenicity in rats

Semaglutide has been concluded teratogenic in rats, with exposure at no observable adverse effect level (NOAEL) below expected human exposure. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function which is specific to rats.

Non-human primates and humans do not depend on a yolk sac with placental function to supply nutrients to the embryo early in pregnancy. The effect on rat embryo-foetal development is therefore not likely to be relevant to humans as described below. Preliminary and main embryo-foetal development and pre- and postnatal development studies with doses corresponding to 12-15 fold expected clinical exposure in cynomolgus monkeys have been finalised. In the main embryo-foetal development study sporadic abnormalities were reported across all dose groups and in the pre- and postnatal development study a dose-dependent increase in early pregnancy losses was observed. The findings observed across the three studies in cynomolgus monkeys are not indicative of a teratogenic potential of semaglutide in this species. The increase in early pregnancy losses is indicative of embryo-toxicity, which may be related to the maternal effect of semaglutide (marked body weight loss). A developmental toxicity NOAEL was determined at an exposure 1- to 2 fold the expected clinical exposure (1 mg/week). A risk for the developing human embryo or foetus cannot be definitely ruled out, but the absence of findings indicative of teratogenicity in the embryo-foetal development and pre- and postnatal development studies in cynomolgus monkey decreases the level of concern.

A comprehensive review of results from the nonclinical studies can be found in the current edition of semaglutide (NN9535) Investigator's Brochure (IB),[26] or any updates hereof.

3.1.5 Clinical data - semaglutide

As of 20 December 2014, six clinical pharmacology trials (trials 1820, 3679, 3633, 3616, 3819 and 4010) and one phase 2 trial (trial 1821) have been completed with semaglutide s.c. In the completed trials, 553 subjects have been exposed to semaglutide: 192 healthy subjects (both single and multiple dosing), 313 subjects with T2D (up to 12 weeks treatment) and 48 subjects with varying

degrees of renal impairment (four with T2D) (single dosing). In addition, 22 healthy subjects have been exposed to semaglutide s.c. in the oral administration semaglutide project (trials NN9924-3691 and NN9924-3692).

As of 20 December 2014, 8 therapeutic confirmatory trials are ongoing with semaglutide s.c. The efficacy and safety of semaglutide s.c. dosing once weekly is compared versus placebo in drug naïve subjects (trial 3623), versus the DPP-4 inhibitor sitagliptin (trial 3626), versus exenatide extended release (trial 3624), versus basal insulin (trial 3625) and versus placebo as add on to basal insulin (trial 3627). In addition, a long-term (104 weeks) trial is ongoing to compare the long-term safety (including cardiovascular risk) and efficacy versus placebo as add-on to standard-of-care treatment (trial 3744). Finally, two trials are being conducted in Japanese subjects with T2D in which the efficacy and safety of semaglutide as monotherapy is compared to sitagliptin monotherapy (trial 4092) and semaglutide (0.5 mg and 1.0 mg) in monotherapy or in combination with one oral antidiabetic drug (OAD) (either of sulfonylurea, glinide, α-glucosidase inhibitor or thiazolidinedione) is compared with OAD therapy in subjects who are insufficiently controlled on diet/exercise therapy or OAD monotherapy (either of sulfonylurea, glinide, α-glucosidase inhibitor or thiazolidinedione) (trial 4091). In parallel, 10 clinical pharmacology trials are ongoing (trials 3817, 3789, 3652, 3685, 3634, 3684, 3651, 3635, 3687 and 3818) to investigate the metabolism of semaglutide, the impact of hepatic impairment on the pharmacokinetic profile of semaglutide and the effect of semaglutide on several aspects of glycaemic control, appetite regulation, QTc-prolongation and drug-drug interaction with selected oral drugs. These investigations are being performed in different populations including healthy subjects, subjects with T2D, obese subjects and subjects with hepatic impairment.

3.1.5.1 Pharmacokinetics

Results from two single dose trials (NN9535-3616 and NN9535-4010) and from one multidose trial (NN9535-3819) based on the LC-MS/MS assay demonstrated a median time to maximum concentration (t_{max}) of 24-96 hours post dosing and a $t_{½}$ in the range of 155-183 hours. Overall, the pharmacokinetic properties of semaglutide appear similar in Caucasian and Japanese subjects and also in healthy subjects and subjects with T2D. In a trial with subjects with different degrees of renal impairment (NN9535-3616), data suggested that subjects with severe renal impairment had a slightly higher exposure compared to subjects with normal renal function. Area under curve ($AUC_{0-\infty}$) increased by approximately 22% in subjects with severe renal impairment whereas subjects with mild or moderate renal impairment and subjects on haemodialysis had exposure similar to subjects with normal renal function. No safety signals were identified in either of the renal groups and tolerability profiles appeared similar across renal groups; thus a dose-reduction in subjects with severe renal impairment does not appear to be warranted.

Interaction with oral contraceptives was assessed at semaglutide 1.0 mg steady-state exposures in postmenopausal women with T2D (NN9535-3819). Steady-state exposures (AUC_{0-24h}) of

ethinylestradiol and levonorgestrel were slightly increased, with bioequivalence criterion met for ethinylestradiol but not for levonorgestrel; the increase was seen when oral contraceptives were coadministered with semaglutide compared to oral contraceptives alone. The bioequivalence criterion was met for maximum concentration (C_{max}) of both ethinylestradiol and levonorgestrel. These data indicate that semaglutide does not decrease the exposure of oral contraceptives, and suggest that no adjustments of oral contraceptive dose are warranted for women of childbearing potential using a low-dose oral contraceptive.

3.1.5.2 Efficacy

As of 20 December 2014, efficacy of semaglutide in the target population - subjects with T2D has been investigated in one phase 2 dose range finding trial (NN9535-1821). The trial was a 12-week, randomised, double-blind, placebo- and active-controlled trial in which 411 adults with T2D received once-weekly s.c. injection of 1 of 5 semaglutide dose levels (0.1-1.6 mg), once-daily injection of open label liraglutide (1.2 mg or 1.8 mg) or once-weekly placebo.

12 weeks of treatment, equivalent to 5-7 weeks in steady state on maintenance dose, provided statistically significant and clinically relevant improvement in glycaemic control for dose levels of 0.2 mg and above. Mean changes in glycosylated haemoglobin (HbA_{1c}) from baseline was up to -1.19% (placebo adjusted estimated treatment difference). Dose-dependent improvements in fasting plasma glucose (FPG) and postprandial PG were also observed. The improvement in glycaemic control was accompanied by weight loss for semaglutide doses of 0.8 mg and above (estimated treatment difference compared to placebo up to a mean value of -3.64 kg).

3.1.5.3 Safety

From the clinical trials completed so far the following safety observations have been made. In consistency with the findings obtained from evaluating other GLP-1 RAs, common adverse events (AEs) included nausea and vomiting; most of them were mild to moderate in severity. Hypoglycaemia has occurred in subjects receiving semaglutide and these events have mainly been minor. As with other GLP-1 RAs, an increase in heart rate has been observed in subjects exposed to semaglutide . The implications of this increase are unknown. As with all protein based pharmaceuticals, subjects treated with semaglutide may develop immunogenic and allergic reactions. Few allergic reactions have been reported in connection with semaglutide. These have mainly been mild and transient however, more generalised reactions may occur, including urticaria, rash, pruritus and rare cases of angioedema have been observed. Injection site reactions have been infrequently reported. These have mainly been mild and transient in nature.

Please see the current edition of semaglutide (NN9535) IB[26] or any updates hereof for further details.

For an assessment of benefits and risks of the trial, see section 18.1.

3.1.6 Dulaglutide

Dulaglutide is a GLP-1 RA with prolonged action developed and marketed by Eli Lilly and Company, IN, US under the trade name Trulicity®. Dulaglutide has recently been approved in the US and in the EU for use as once-weekly s.c. injection for treatment of T2D. Dulaglutide has shown non-inferiority on glycaemic control versus liraglutide, but significantly less weight loss.[27]

Dulaglutide belongs to the same class of drugs as semaglutide and as such they share many of the same efficacy and safety characteristics. As dulaglutide is a marketed drug its characteristics are described in the EU summary of product characteristics (SmPC),[28] US prescribing information[29] and the local prescribing information (non-US and non-EU countries) for dulaglutide (Trulicity®).

3.2 Rationale for the trial

The currently available treatment modalities for T2D are still not satisfactory and there is a large proportion of subjects not reaching the treatment targets despite a high level of compliance with the treatment regimens. Furthermore, there is a segment of subjects where either compliance with once-daily treatment regimens is an issue resulting in sub-optimal glycaemic control, or where there is a wish for a more convenient treatment regimen.

The aim for the present trial is to compare semaglutide once-weekly versus dulaglutide once-weekly as addition to metformin in a population of subjects with T2D in terms of glycaemic control, weight control and other efficacy parameters. Furthermore, the trial is designed to address and compare tolerability, patient well-being and treatment satisfaction.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

Primary objective

To compare the effect of once-weekly dosing of two dose levels of s.c. semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of two dose levels of s.c. dulaglutide (0.75 mg and 1.5 mg) on glycaemic control in subjects with T2D on a background treatment with metformin.

Secondary objective

To compare the effect of once-weekly dosing of two dose levels of s.c. semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of two dose levels of s.c. dulaglutide (0.75 mg and 1.5 mg) in subjects with T2D on a background treatment with metformin with regards to:

- Body weight control
- Blood pressure and fasting blood lipids
- Patient reported outcomes
- Safety and tolerability

4.2 Endpoint(s)

4.2.1 Primary endpoint

- Change from baseline to week 40 in HbA_{1c}

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoint

- Change from baseline to week 40 in body weight (kg)

4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

Change from baseline to week 40 in:

- FPG*
- Self-measured plasma glucose (SMPG), 7-point profile
    - Mean 7 point profile
    - Mean post prandial increment (over all meals)
- Fasting blood lipids (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides)
- BMI and waist circumference

- Systolic and diastolic blood pressure*
- Overall scores for patient reported outcomes
    - Short Form health survey (SF-36v2™)
    - Diabetes Treatment Satisfaction Questionnaire (DTSQ)*

Subjects who after 40 weeks treatment achieve (yes/no):

- HbA_{1c} <7.0% (53 mmol/mol) American Diabetes Association (ADA) target
- HbA_{1c} ≤6.5% (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target*
- Weight loss ≥5%
- Weight loss ≥10%
- HbA_{1c} <7.0% (53 mmol/mol) without severe or BG confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA_{1c} reduction ≥1%
- Weight loss ≥3%
- HbA_{1c} reduction ≥1% and weight loss ≥3%

Supportive secondary safety endpoints

- Number of treatment emergent adverse events (TEAEs)
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemia episodes
- Treatment emergent severe or BG confirmed symptomatic hypoglycaemia episodes (yes/no)

Change from baseline to week 40 in:

- Haematology
- Biochemistry
- Calcitonin
- Pulse
- Electrocardiogram (ECG) category
- Physical examination

* Key supportive secondary endpoint prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT)

5 Trial design

5.1 Type of trial

The trial is a 40-week randomised, open-label, active-controlled, parallel group, multicentre, multinational, four-armed trial.

Subjects with T2D inadequately controlled with metformin alone will after approximately 2 weeks screening period be randomised in a 1:1:1:1 manner to receive either a dose of 0.5 mg or 1.0 mg of semaglutide once-weekly or 0.75 mg or 1.5 mg of dulaglutide once-weekly.

After the treatment period of approximately 40 weeks in total, all subjects enter a follow-up period of 5 weeks ended by a follow-up phone contact. Total trial duration for the individual subjects will be approximately 47 weeks. The trial design is summarised schematically in Figure 5–1.

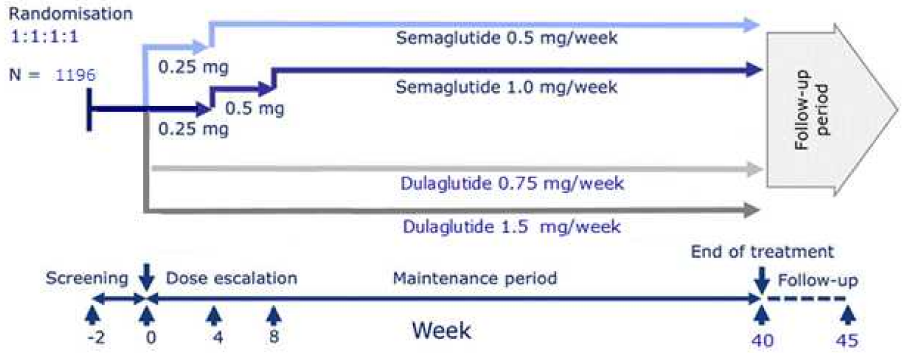


Figure 5–1 Trial design

5.2 Rationale for trial design

The aim for the trial is to compare the efficacy of semaglutide 0.5 mg once-weekly versus dulaglutide 0.75 mg once-weekly and the efficacy of semaglutide 1.0 mg once-weekly versus dulaglutide 1.5 mg once-weekly in subjects with T2D in terms of glycaemic control, weight control and other efficacy parameters. Furthermore, the trial is designed to address and compare tolerability, patient well-being and treatment satisfaction. The in- and exclusion criteria allow for enrolment of a broad trial population and include subjects with mild renal impairment. The treatment duration of 40 weeks is considered adequate for assessment of efficacy, safety, tolerability and patient satisfaction.

5.3 Treatment of subjects

Semaglutide treatment

Subjects randomised to semaglutide will follow a fixed dose escalation. The maintenance dose of 0.5 mg will be reached after 4 doses (4 weeks) of 0.25 mg. The maintenance dose of 1.0 mg will be reached after 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg. After the maintenance dose is reached, the dose must not be changed during the course of the trial unless due to safety reasons.

Dulaglutide treatment

Subjects randomised to dulaglutide will receive a dose of either 0.75 mg or 1.5 mg dulaglutide once-weekly without dose escalation. The randomisation dose must not be changed during the course of the trial unless due to safety reasons.

Table 5–1 Treatment of subjects

Trial periods		**Screening**	**Treatment**	**Treatment**	**Treatment**	**Follow-up**
Duration of each period		2 weeks	4 weeks	4 weeks	32 weeks	5 weeks
Treatment arm	**N**					
Semaglutide 0.5 mg	299	Screening	Semaglutide 0.25 mg	Semaglutide 0.5 mg	Semaglutide 0.5 mg	Follow-up
Semaglutide 1.0 mg	299	Screening	Semaglutide 0.25 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Follow-up
Dulaglutide 0.75 mg	299	Screening	Dulaglutide 0.75 mg	Dulaglutide 0.75 mg	Dulaglutide 0.75 mg	Follow-up
Dulaglutide 1.5 mg	299	Screening	Dulaglutide 1.5 mg	Dulaglutide 1.5 mg	Dulaglutide 1.5 mg	Follow-up

5.3.1 Background medication

The only allowed diabetes background medication is metformin. Subjects must upon inclusion continue pre-trial dose of background medication throughout the entire trial unless the subject meets the rescue criteria, see section 6.4.

Metformin

Metformin is considered background medication and will not be provided by Novo Nordisk A/S. Metformin should be used in accordance with standard of care in the individual country at the discretion of the investigator. However, the maximum approved dose in the individual country must not be exceeded.

Only applicable for Slovakia: All antidiabetic medication will be reimbursed by Novo Nordisk Slovakia s.r.o.

5.3.2 Injection site

Injections should be administered in the thigh, abdomen or upper arm, at any time of the day irrespective of meals. Injections should be administered on the same day of the week during the trial. Injections should not be administered intravenously or intramuscular.

5.3.3 Missed dose

If a semaglutide dose is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (48 hours). If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the subject should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week.

If a dulaglutide dose is missed, it should be administered as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose. If less than 3 days (72 hours) remain before the next scheduled dose, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, subject can then resume their regular once weekly dosing schedule.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products the subject should be switched to a suitable marketed product at the discretion of the investigator.

5.5 Rationale for treatment

Semaglutide has been developed for s.c. administration. The doses of 0.5 mg and 1.0 mg once-weekly have been chosen based on careful evaluation to strike a satisfactory balance of efficacy and safety that would satisfy the majority of subjects. Hence, the duration and the dose of the randomised treatments are considered adequate for obtaining meaningful information on efficacy and safety in accordance with the trial objectives. Subjects will enrol for a treatment period of 40 weeks in order to be able to evaluate full effect and durability of the primary and secondary endpoints as well as reasonable safety assessment.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened:	1994
Number of subjects planned to be randomised:	1196
Number of subjects expected to complete the trial*:	897

*Number of subjects expected to complete the trial on randomised trial product without rescue medication.

6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered “yes”.

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age ≥ 18 years at the time of signing informed consent
3. Subjects with T2D diagnosed clinically ≥ 90 days prior to screening
4. HbA_{1c} 7.0 – 10.5% (53 – 91 mmol/mol) (both inclusive)
5. Subjects on stable diabetes treatment with metformin (minimum of 1500 mg/day or maximal tolerated dose documented in the patient medical record) for 90 days prior to screening

6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial product(s) or related products
2. Previous participation in this trial. Participation is defined as signed informed consent
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice). *Germany: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or sexual abstinence or vasectomised partner. Ireland: Adequate contraceptive measures are defined as established use of combined oral contraceptives, injected or implanted hormonal methods of contraception, sterilisation, intrauterine device or intrauterine system or consistent use of barrier methods together with the use of spermicide and sexual abstinence. United Kingdom: Adequate contraceptive measures are defined as established use of oral, intravaginal, transdermal combined estrogen and progestogen hormonal methods of contraception; oral, injected or implanted progestogen only hormonal*

methods of contraception; placement of an intrauterine device or intrauterine hormone releasing system, bilateral tubal occlusion, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), female sterilisation, vasectomised partner (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle).

4. Receipt of any investigational medicinal product within 90 days before screening
5. Any condition, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol
6. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening. An exception is short-term insulin treatment for acute illness for a total of ≤14 days
7. History of pancreatitis (acute or chronic)
8. Screening calcitonin ≥50 ng/L
9. Family or personal history of Multiple Endocrine Neoplasia Type 2 or Medullary Thyroid Carcinoma
10. Renal impairment defined as eGFR < 60 mL/min/1.73 m^2 as per CKD-EPI
11. Any of the following: myocardial infarction (MI), stroke or hospitalisation for unstable angina and/or transient ischaemic attack (TIA) within the past 180 days prior to the day of screening
12. Subjects presently classified as being in New York Heart Association (NYHA) Class IV
13. Planned coronary, carotid or peripheral artery revascularisation on the day of screening
14. Proliferative retinopathy or maculopathy requiring acute treatment
15. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas)
16. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days or on a frequent basis) known to affect weight or glucose metabolism (e.g. orlistat, thyroid hormones, corticosteroids)

6.4 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification. If any of the FPG values exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified, a confirmatory FPG should be obtained by the central laboratory by calling the subject for a re-test as soon as possible:

- 15.0 mmol/L (270 mg/dl) from week 2 to end of week 7
- 13.3 mmol/L (240 mg/dl) from week 8 to end of week 13
- 11.1 mmol/L (200 mg/dl) from week 14 to end of treatment

If the confirmatory FPG also exceeds the values described above, the subject should be offered rescue medication in accordance with ADA/European Association for the Study of Diabetes[30] (excluding GLP RAs, DPP-4 inhibitors and amylin analogues). It is important for trial integrity that

only subjects actually needing treatment intensification (as defined above) are started on rescue medication. Rescue medication (intensification of existing background medication and/or initiation of new antidiabetes medication) and any changes hereto should be captured on the concomitant medication form in the electronic case report form (eCRF), see section 8.2.4. Rescue medication should be prescribed as add-on to randomised treatment and subjects should continue to follow the protocol-specified visit schedule.

6.5 Premature discontinuation of trial product criteria

If any of the below trial product discontinuation criteria apply, the subject must be discontinued from trial product. The procedures in section 8.1.6 should be performed and the subject will not be withdrawn from the trial.

The subject must discontinue from trial product if the following applies:

- In case of pregnancy or intention to become pregnant
- A subject included in the trial in violation of the inclusion and/or exclusion criteria
- Simultaneous participation in any other clinical trial receiving an investigational medicinal product
- Due to a safety concern at the discretion of the investigator
- Calcitonin value ≥50 ng/L

The primary reason for discontinuation of trial product must be specified in the eCRF.

6.6 Withdrawal reason

The subject may withdraw at will at any time. The subject's request to discontinue must always be respected.

- Withdrawal of informed consent

Please see section 8.1.7 for procedures to be performed in case of subject withdrawal.

6.7 Subject replacement

Subjects who are withdrawn, initiated rescue medication or prematurely discontinue will not be replaced

6.8 Rationale for trial population

Subjects with T2D who are inadequately controlled on metformin will be included in the trial. Only serious concomitant conditions which could interfere with trial schedule and procedures preclude subjects from participating. The in- and exclusion criteria allow for enrolment of a broad trial population and include subjects with mild renal impairment.

7 Milestones

Planned duration of recruitment period (FPFV– LPFV): 24 weeks

Planned date for FPFV: 06-Jan-2016

Planned date for LPLV: 24-May-2017

End of trial is defined as LPLV.

Recruitment:
The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure,[31] it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors,[32] the Food and Drug Administration Amendment Act,[33] European Commission Requirements[34,35] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

The following sections describe the assessments and procedures. These are also included in the flow chart (see section 2) as well as visit numbers, timing of site and phone visits and visit windows during the trial period.

Informed consent must be obtained before any trial related activity, see section 18.2.

A completion session must be performed in the IWRS after completion of V9.

8.1.1 Investigator site log

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list and may be generated from IWRS.

In addition, the investigator must keep a log of staff and a delegation of task(s) list at the trial site. Investigator must sign the log of staff and the delegation of task(s) at the trial site prior to the delegation of tasks.

8.1.2 Screening, visit 1

At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

8.1.3 Screening failures

For screening failures the screening failure form in the case report form (CRF) must be completed with the reason for not continuing in the trial. Serious adverse events (SAEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up of SAEs must be carried out according to section 12.

A screening failure session must be made in the IWRS and the screening failure form completed in the eCRF. The case book must be signed.

8.1.4 Re-screening

Re-screening is NOT allowed.

8.1.5 Fasting visits

The subjects should attend site visits in a fasting state (see section 2 for details). Fasting is defined as having consumed only water within the last 6 hours prior to the visit. Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed but other prescribed medication should be taken according to prescription.

If the subject does not attend the visit in a fasting state, the subject should be asked to attend a re-scheduled visit within the visit window to have the fasting assessments performed.

8.1.6 Premature discontinuation of trial product

If a subject is prematurely discontinued from trial product, the investigator must aim to undertake procedures similar to those for visit 9A (end of treatment) as soon as possible and the follow-up phone contact (phone contact 10A) should be performed five weeks after premature treatment discontinuation (+ 7 days).

Subjects discontinuing trial product prematurely should continue with the scheduled site contacts after visit 9A has been conducted. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after discontinuation of trial product. Furthermore, subjects prematurely discontinued from trial product must be asked to attend the planned visit (visit 9) taking place 40 weeks (± 7 days) after their randomisation date and the planned phone contact (phone contact 10) five weeks later (+ 7 days).

If the subject is not willing to attend one or more of the above mentioned visits, it should be documented in the subject's medical record that the subject has refused to attend the visit.

For subjects prematurely discontinued from trial product, final drug accountability must be performed and a treatment discontinuation session must be made in the IWRS. The reason for premature discontinuation of trial product must be recorded in subject's medical records and the eCRF.

8.1.7 Withdrawals

If a subject considers to withdraw from the trial, the investigator must aim to undertake procedures similar to those for visit 9A (end of treatment) as soon as possible and the follow-up phone contact (phone contact 10A) should be performed five weeks after premature treatment discontinuation (+ 7 days). If a subject has already prematurely discontinued from trial product and previously attended visit 9A (end of treatment) and follow-up phone contact (10A), no further visits should be attended.

For withdrawn subjects, the end-of-trial form including the primary reason for premature discontinuation of trial product must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be

made in the IWRS, however if a subject has already prematurely discontinued from trial product and a treatment discontinuation session in IWRS has been done, no IWRS session should be completed. The case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

8.1.8 Investigator assessment

Review of diaries, PROs, laboratory reports, ECGs, fundoscopy/fundus photography, physical examination etc. must be documented with the investigator's or delegate's dated signature either on the front page of the documents and/or in the subject's medical record. The signed documents must be retained at the trial site as source documentation.

For ECGs, physical examinations and fundoscopy/fundus photography the evaluations must follow the categories:

- Normal
- Abnormal
  - Was the result clinically significant? (No/Yes)

The evaluation should be based on investigator's or delegate's judgment.

For laboratory report values outside the reference range, the investigator must specify whether the value is clinically significant or clinically non-significant. All laboratory printouts must be signed and dated by the investigator on the day of evaluation. The signed laboratory report is retained at the trial site as source documentation.

In case of abnormal clinical significant findings found as a result of screening procedures conducted at visit 1 or assessments revealing baseline conditions at visit 2, the investigator must state a comment in the subject's medical record and record this in the concomitant illness form in the eCRF. At subsequent visits, any clinically significant changes or new clinically significant findings must be reported as an AE according to section 12.

Investigator or trial site staff must review the diary to ensure that AEs, including overall change in health and concomitant medication, are reported.

If clarification of entries or discrepancies in the diary or PRO is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

8.2 Subject related information

8.2.1 Demography

Demography will be recorded at screening visit and consists of:

- Date of birth (according to local regulation)
- Sex
- Race (according to local regulation)
- Ethnicity (according to local regulation)

8.2.2 Tobacco use

Details of tobacco use must be recorded at the screening visit. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked.

8.2.3 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial as described in section 8.1.8.

Medical history is a medical event that the subject has experienced in the past. Only relevant medical history as judged by the investigator should be reported.

The information collected for concomitant illness and medical history should include diagnosis, onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

8.2.3.1 Diagnosis of diabetes

The date of diagnosis of T2D will be recorded at the screening visit.

8.2.3.2 History of cardiovascular disease

Information related to history of cardiovascular disease (i.e. heart failure including NYHA class, hypertension or ischaemic stroke) or other risk factors for cardiovascular disease will be recorded in the eCRF at screening visit.

8.2.3.3 History of gallbladder disease

Information related to history of gallbladder disease (i.e. gallstone disease, cholecystitis) will be recorded in the eCRF at screening visit.

8.2.4 Concomitant medication

A **concomitant medication** is any medication, other than the trial product, which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at the first visit (screening visit). Changes in concomitant medication, including antidiabetic treatment prescribed at the end of the treatment and rescue treatment, must be recorded at each visit as they occur and the eCRF should be updated accordingly.

The information collected for each concomitant medication includes trade name or generic name, indication, start date (only start year is applicable if more than one year) and stop date or continuation and total daily dose (applicable only for antidiabetic medication).

If a change is due to an AE, then this must be reported according to section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.3 Assessments for efficacy

8.3.1 Height, body weight and BMI

Height is measured without shoes in cm or inches and recorded to nearest ½ cm or ¼ inch.

Body weight should be measured without shoes and only wearing light clothing to the nearest kg/lb.

BMI will be calculated in the eCRF every time the weight is measured using the equation:

BMI = body weight (kg)/(height (m) x height (m)) [kg/m^2 = lb/in^2 x 703]

8.3.2 Waist circumference

The waist circumference is defined as the minimal abdominal circumferences located midway between the lower rib margin and the iliac crest.

The measurement of waist circumference should be performed and recorded in the eCRF. The waist circumference will be measured using a non-stretchable measuring tape. It should be recorded to the nearest ½ cm or ¼ inch using the same measuring tape throughout the trial.

The waist circumference should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The tape should touch the skin but not compress soft tissue. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

8.3.3 Blood pressure

Systolic and diastolic blood pressure should be measured in a sitting position after the subject has been resting for at least 5 minutes and by using the standard clinical practice at the trial site.

8.3.4 Blood samples

Blood samples will be drawn according to flow chart and analysed at the central laboratory to determine levels of the following efficacy laboratory parameters:

Glucose metabolism:

- HbA_{1c} and FPG

Lipids (all fasting):

- Total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides

8.3.5 Self-measured plasma glucose

At the screening visit, subjects will be provided with a blood glucose meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use. The subjects will be instructed in how to use the device, the instruction will be repeated as necessary during the trial.

The blood glucose meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

Subjects should be instructed in how to record the results of the SMPGs in the diaries. The record of each SMPG should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF should be corrected.

8.3.6 7-point self-measured plasma glucose profile

The subject will be asked to perform a 7-point SMPG profile, preferably within one week prior to site visit according to the flowchart, on days where the subject does not anticipate unusual strenuous exercise.

Time points, including date and time, for the 7-point profile: before breakfast, 90 min after start of breakfast, before lunch, 90 minutes after start of lunch, before dinner, 90 min after start of dinner and at bedtime

8.4 Assessments for safety

8.4.1 Physical examination

A physical examination must be performed and include the following:

General appearance, skin, thyroid gland, respiratory system, cardiovascular system, gastrointestinal system including mouth, central and peripheral nervous system, and lymph node palpation

8.4.2 Pulse

Pulse (beats per minute) should be recorded at site visits after resting for 5 minutes in a sitting position.

8.4.3 Electrocardiogram – 12 lead

A 12-lead ECG must be performed and interpreted locally by the investigator as described in section 8.1.8.

It is allowed to perform the screening visit ECG between the screening visit and the randomisation visit. The results must be available prior to randomisation. An ECG performed for any reason unrelated to this trial within 7 days prior to the screening visit is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime.

If the ECG was performed as a part of routine clinical practice on/before the date when the subject has signed the informed consent, it must be documented in the medical records that the reason for performing the procedure is not related to this trial.

8.4.4 Fundoscopy/fundus photography

Fundoscopy/fundus photography will be performed by the investigator or a local ophthalmologist according to local practice. Result of the fundoscopy/fundus photography will be interpreted by the investigator as described in section 8.1.8. Dilation is not a requirement.

If a fundoscopy/fundus photography has been performed within 90 days prior to randomisation, the procedure does not need to be repeated, unless worsening of visual function since the last examination has been noted.

If the fundoscopy/fundus photography was performed as a part of routine clinical practise on/before the date when the subject has signed the informed consent, it must be documented in the medical records that the reason for performing the procedure was not related to this trial.

8.4.5 Blood samples

Blood samples will be drawn and analysed at the central laboratory to determine levels of the following laboratory parameters:

Biochemistry:

- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, bilirubin (total), alkaline phosphatase, potassium, sodium, calcium (total), amylase, lipase, calcitonin and creatinine, including eGFR (per CKD-EPI)

Haematology:

- Haemoglobin, haematocrit, erythrocytes, thrombocytes and leucocytes

Pregnancy test (females of child bearing potential):

- Serum beta-human chorionic gonadotropin

8.4.6 Pregnancy test

Females of childbearing potential will have a serum pregnancy test (beta-human chorionic gonadotropin) performed. At the randomisation visit, a urine pregnancy test must be performed prior to randomisation.

In case a menstrual period is missed or if pregnancy is suspected at any time during the trial, a urine pregnancy test should be performed. The subject should be instructed not to dose trial product before pregnancy has been ruled out.

Pregnancy testing will not be required (unless required by local law) for women of non-childbearing potential, such as but not limited to women who have undergone a hysterectomy, bilateral oophorectomy, bilateral tubal ligation or are postmenopausal (e.g. women above the age of 50, who have been without menstrual period for at least 1 year).

8.4.7 Calcitonin

Blood samples for the measurement of calcitonin concentration will be drawn as per flow chart. In case any calcitonin value at any time of the trial is >10 ng/L, the algorithm in appendix B should be followed.

8.4.8 Hypoglycaemic episodes

BG should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose values:

- ≤ 3.9 mmol/L (70 mg/dL) or
- > 3.9 mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms

should be recorded by the subject, except for P10/P10A (see section 8.6.1). These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from visit 1 to phone contact 10.

The record should include the following information:

- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available)
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself
- Date and time and of last trial product administration and other antidiabetic drug(s) administered prior to the episode
- Date and time of last main meal prior to episode
- Whether the episode occurred in relation to physical activity
- Any sign of fever or other disease
- Whether the subject was asleep when the episode occurred
  - If yes, whether the symptoms of the episode woke up the subject

The answer to the question: "Was subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration[36].

Oral carbohydrates should not be given if the subject is unconscious.

If the question "Was subject able to treat him/herself?" is answered "No", the following information should be recorded:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. family/friend/co-worker or similar, paramedic, doctor or other, please specify)
- Where the treatment was administered (i.e. at home/at friends/at work or similar, in an ambulance, emergency room/hospital or other, please specify)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other, please specify)
- Were symptoms alleviated after administration of treatment?

- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), other factors not listed, please specify or none)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms?[37]
  - Autonomic: sweating, trembling, hunger or palpitations
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination
  - General malaise: headache or malaise
- Did the subject experience other symptoms? Please specify
- Description of the episode, if applicable

A hypoglycaemic episode form must be filled in for each hypoglycaemic episode. If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must also be filled in, see section 12.

8.5 Laboratory assessments

The laboratory analyses will be performed by a central laboratory. If collected, anti-semaglutide antibody and IgE antibodies will be analysed by Novo Nordisk A/S. The central laboratory may utilise subcontractors. In the events described in section 8.7, a local laboratory must be used. Descriptions of assay methods, laboratory supplies and procedures for collecting, handling, storage and shipping of samples, will be described in the laboratory manual provided by the central laboratory.

Laboratory samples not drawn on the day of the actual visit should preferably be drawn on another day within the visit window stated in the flow chart. For some of the samples drawn during the trial, subjects will be asked to attend the relevant site visits fasting (see section 8.1.5).

Laboratory results will be sent by the central laboratory to the investigator on an on-going basis and the investigator must review all laboratory results for signs of concomitant illness and AEs and report these according to this protocol (see section 12).

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal

values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

All laboratory samples will be destroyed at the latest at the completion of the clinical trial report.

8.6 Other assessments

8.6.1 Subject diary

The subject must be provided with paper diaries at visits described in the flow chart. Entries in the diaries are only to be made by the subject, unless otherwise specified.

The investigator should instruct the subject in recording the following data in the diary:

- Date, time and dose of first dose of trial product
- Date and last dose of trial product prior to each visit
- SMPG 7-point profile
- Hypoglycaemic episodes
- Concomitant medication
- AEs

The diaries should be handed out/collected as indicated in the flow chart. The subject should bring the diary for review at every clinic visit during the trial. The recordings must be reviewed as described in section 8.1.8 and transcribed to the eCRF.

If any hypoglycaemic events are reported at P10 or P10A, the information related to the hypoglycaemic event(s) should be documented in the subject's medical record and the entry in the medical record will be considered source data.

8.6.2 Patient reported outcome questionnaires

The following PRO questionnaire will be used in the trial:

- SF-36v2™
- DTSQs

The questionnaires should be completed by the subject, preferably after conclusion of all fasting related activities but before any other visit-related activities. It takes approximately 10 minutes to complete the questionnaires. The assessments must be reviewed as described in section 8.1.8. All results from the PRO questionnaires must be transferred into the eCRF. Please refer to appendix A for details on the PRO questions.

The SF-36v2™ questionnaire will be used to assess subjects overall health related quality of life and can also be used to estimate quality adjusted life years (QALY) which is used in cost

effectiveness calculations. This questionnaire contains 36 items and measures the individual overall health related quality of life on 8 domains; physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

The DTSQs questionnaire will be used to assess subject's treatment satisfaction. This questionnaire contains 8 items and measures the subject's diabetes treatment (including insulin, tablets and/or diet) in terms of convenience, flexibility and general feelings regarding treatment.

8.6.3 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

Treatment compliance: will be assessed by monitoring of drug accountability. Prior to visits where drug accountability is performed the subject will be asked to return all used, partly used and unused trial products. The investigator must assess the amount of trial products returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject.

8.7 Adverse events with additional data collection

For some AEs, additional data collection is required and special forms must be completed in the eCRF, see section 12. The AEs with additional data collection are:

- Cardiovascular events
- Pancreatitis
- Thyroid disease
- Neoplasm
- Hypersensitivity reactions

Selected events (cardiovascular events, pancreatitis, thyroid disease and neoplasm) will be adjudicated and for further details on the definitions, please refer to Table 12–2.

In case any of these events fulfil the criteria for an SAE, this must be reported according to section 12.1.

Acute coronary syndrome

If an event of acute coronary syndrome is observed during the trial, the following information must be reported in the eCRF, if available:

- Duration of symptoms
- Changes in ECG
- Collection of cardiac biomarkers
- Cardiac imaging
- Cardiac stress testing
- Angiography
- Use of thrombolytic drugs
- Coronary Revascularisation procedures

Cerebrovascular events

If a cerebrovascular event is observed during the trial, the following information must be reported in the eCRF, if available:

- Type of event
- Contributing condition
- Neurologic signs and symptoms
- History of neurologic disease
- Imaging supporting the condition
- Treatment given for the condition

Heart failure requiring hospitalisation

If an event of heart failure requiring hospitalisation is observed during the trial, the following information must be reported in the eCRF, if available:

- Signs and symptoms of heart failure
- NYHA Class
- Supportive imaging
- Supportive laboratory measurements
- Initiation or intensification of treatment for this condition

Pancreatitis

In case of a suspicion of acute pancreatitis, the trial product should promptly be interrupted until pancreatitis is ruled out. Appropriate additional examinations must be performed, including local measurement of amylase and lipase.

Appropriate treatment and careful monitoring of the subject should be initiated if pancreatitis is confirmed as a minimum 2 out of the following 3 criteria:

- Severe acute abdominal pain
- Amylase and/or lipase >3x upper normal range (UNR)
- Characteristic findings on relevant imaging e.g. computerised axial tomography (CT)/magnetic resonance imaging (MRI)/ultrasound)

If acute pancreatitis is ruled out, trial product should be re-initiated. If acute pancreatitis is confirmed, the subject must be prematurely discontinued from trial product and should remain in the trial, please refer to sections 6.5 and 8.1.6.

If an event of pancreatitis is observed during the trial, the following information must be reported in the eCRF, if available:

- Signs and symptoms of pancreatitis
- Specific laboratory tests supporting a diagnosis of pancreatitis: amylase, lipase, bilirubin, alkaline phosphatase, ALT and AST
- Imaging performed and consistency with pancreatic disease
- Treatment for and complications of the event
- Relevant risk factors for pancreatic disease including
  - History of gallstones
  - History of pancreatitis
  - Family history of pancreatitis
  - Trauma

Thyroid disease

If an event of thyroid disease, including any thyroid neoplasms observed during the trial, the following information must be reported in the eCRF, if available:

- History of thyroid disease
- Signs and symptoms leading to investigations of thyroid disease
- Specific laboratory tests describing thyroid function: thyroid-stimulating hormone (TSH), calcitonin, thyroid peroxidase antibodies, thyroglobulin and thyroglobulin antibody, TSH receptor antibody, and total and free T3 and T4 and Free Thyroid Index
- Diagnostic imaging performed and any prior imaging supporting the disease history
- Pathologic examinations
- Treatment given for the condition
- Risk factors identified
- Family history of thyroid disease

Neoplasm

All events of neoplasms (excluding thyroid neoplasm, which will be reported under thyroid disease) must be reported during the trial. The following information should be obtained, if available:

- Type of neoplasm
- Symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment for the event
- Participation in screening programs
- Risk factors associated to the event

Hypersensitivity reactions

In case of suspicion of a hypersensitivity reaction, the subjects should be instructed to contact the trial site staff as soon as possible for further guidance.

All events of hypersensitivity reactions (including allergic reactions, immune complex disease and anti-semaglutide antibody formation) must be reported and the following information must be obtained, if available:

- Signs and symptoms associated with the event
- Time of appearance after administration of trial drug
- Relevant immunological tests performed
- Treatment given for the reaction
- Previous history of similar reactions
- Risk or confounding factors identified

Severe immediate hypersensitivity reaction

In case of suspicion of a severe immediate hypersensitivity reaction to the trial product is suspected, the subject must be prematurely discontinued from trial product and should remain in the trial, please refer to sections 6.5 and 8.1.6.

To assist in diagnosis, it is recommended to draw a blood sample for measurement of tryptase (total and/or mature tryptase, local assessment) within 3 hours of the hypersensitivity reaction, and if this is achieved, a tryptase sample should be collected after a suitable washout period (minimum 5 weeks). Tryptase concentrations should be included in the specific event forms when reporting the AE.

Furthermore, a blood sample for assessment of anti-semaglutide IgE antibodies and anti-semaglutide binding antibodies should be collected after a suitable washout period (minimum 5 weeks).

Immune complex disease

In case of suspicion of immune complex disease, the subject must be prematurely discontinued from trial product and should remain in the trial, please refer to sections 6.5 and 8.1.6. It is recommended to draw a blood sample for local assessment of complement levels (C3 and C4) to assist in diagnosis. Complement level results should be included in the specific event forms when reporting the AE.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the Trial Materials Manual.

Trial products must not be dispensed to any person not included in the trial.

Trial products must not be used, if it does not appear clear and colourless.

9.1 Trial products

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

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Semaglutide	1.34 mg/mL	Solution for injection	s.c.	PDS290 pen-injector
Dulaglutide	0.75 mg/0.5 mL	Solution for injection	s.c.	Pre-filled pen
Dulaglutide	1.5 mg/0.5 mL	Solution for injection	s.c.	Pre-filled pen

Metformin is considered non-investigational medicinal product and will not be supplied by Novo Nordisk A/S.

Only applicable for Slovakia: All antidiabetic medication will be reimbursed by Novo Nordisk Slovakia s.r.o.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13,[38] local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS.

The investigator must document that the DFU is given to the subject orally and in writing at the first dispensing visit (randomisation visit).

9.3 Storage

Table 9–2 Storage of trial products

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
Semaglutide 1.34 mg/mL	Store in refrigerator (2°C-8°C) (US: 36°F-46°F) Do not freeze Protect from light	Store below 30°C (US: 86°F) Do not refrigerate, Do not freeze Protect from light	Use within 1 month
Dulaglutide 0.75 mg/0.5 mL	Store in refrigerator (2°C-8°C) (US: 36°F-46°F) Do not freeze, Protect from light May be stored for up to 12 days not above 30°C (US: 86°F)	N/A (For single use)	N/A (For single use)
Dulaglutide 1.5 mg/0.5 mL	Store in refrigerator (2°C-8°C) (US: 36°F-46°F) Do not freeze, Protect from light May be stored for up to 12 days not above 30°C (US: 86°F)	N/A (For single use)	N/A (For single use)

* In-use time starts when first dose is taken.

The investigator must ensure the availability of proper storage conditions, and also record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range).

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator.

Returned trial product (used/partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product. Drug accountability should be performed at pen level.

Destruction will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented.

9.5 Auxiliary supplies

The following auxiliary supplies will be supplied by Novo Nordisk in accordance with the Trial Materials Manual:

- Needles for PDS290 pen-injector
- DFU for PDS290 pen-injector
- DFU for pre-filled pen
- BG meters and BG meter auxiliaries

10 Interactive web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure

The trial is an open-label trial. A randomisation session will be performed for all eligible subjects by using the IWRS.

At the randomisation visit, eligible subjects will be randomised to one of the four parallel treatment groups in a 1:1:1:1 manner.

- Semaglutide 0.5 mg/week
- Semaglutide 1.0 mg/week
- Dulaglutide 0.75 mg/week
- Dulaglutide 1.5 mg/week

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

Adverse event

An AE is any untoward medical occurrence in a subject administered a product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.4.8.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild** - no or transient symptoms, no interference with the subject's daily activities.
  - **Moderate** - marked symptoms, moderate interference with the subject's daily activities.
  - **Severe** - considerable interference with the subject's daily activities; unacceptable.

- **Causality**

Relationship between an AE and the relevant trial product(s):

- **Probable** - Good reason and sufficient documentation to assume a causal relationship.
- **Possible** - A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** - The event is most likely related to aetiology other than the trial product.

- **Final outcome**
  - **Recovered/resolved** - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
  - **Recovering/resolving** - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
  - **Recovered/resolved with sequelae** - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
  - **Not recovered/not resolved** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
  - **Fatal** - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
  - **Unknown** - This term is only applicable if the subject is lost to follow-up.

Serious adverse event

A SAE is an experience that at any dose results in any of the following:

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening[a] or require hospitalisation[b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE[d].

Suspicion of transmission of infectious agents via the trial product must always be considered an SAE.

[a]. The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

[b]. The term "hospitalisation" is used when a subject:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

[c]. A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

[d]. For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasiasis or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

Medical event of special interest

A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus as required by health authorities. A MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined MESI criteria.

1. Medication errors concerning trial products:
   - Administration of wrong drug or use of wrong device.
     Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in administration of wrong drug.
   - Wrong route of administration, such as intramuscular instead of s.c.
   - Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
   - Accidental administration of a lower or higher dose than intended. However, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen, as judged by the investigator, although they did not necessarily occur.

Adverse events with additional data collection

AEs with additional data collection are AEs defined as critical for the evaluation of safety. Some of these events will furthermore be adjudicated by an external independent committee as described in section 12.7.2.

The AEs that require additional data collection are listed in Table 12–1 below. For further information about event adjudication and events that require additional data collection, please see sections 12.7.2 and 8.7, respectively.

Table 12–1 Adverse events with additional data collection

Event	Event adjudication	Special eCRF form
Fatal event	Yes	No
Acute coronary syndrome	Yes	Yes
Cerebrovascular event	Yes	Yes
Heart failure requiring hospitalisation	Yes	Yes
Pancreatitis	Yes	Yes
Thyroid disease (including thyroid neoplasm)	Yes, (only if thyroid neoplasm or resulting in thyroidectomy)	Yes
Malignant neoplasm (excluding thyroid neoplasm)	Yes	Yes
Hypersensitivity reactions	No	Yes

Technical complaint

A technical complaint is any written, electronic, or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- The packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (P10). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the subject must be asked about AEs and technical complaints, for example by asking: "Have you experienced any problems since the last contact?"

All AEs, either observed by the investigator or subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents:

- Semaglutide: NN9535 IB (section 7.3.2) current version[26] and any updates thereto
- Dulaglutide (Trulicity®): Current version of the EU SmPC[28] and U.S. Food and Drug Administration (FDA) prescribing information[29] and any updates thereto

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

MESIs, regardless of seriousness, must be reported using both the AE form, the safety information form and a medication error form. The medication error form is a form tailored to collect specific information related to the individual MESI.

AEs with additional data collection must be reported using both AE form and specific additional data collection form. The additional data collection form is a form tailored to collect specific information related to the individual event, see section 8.7

For AEs qualifying for event adjudication, the Event Adjudication form will also have to be completed in the eCRF. The Event Adjudication form is a checklist of clinical data to be provided from the site.

The AE form for a non-serious AE not fulfilling the MESI criteria or additional data collection criteria should be signed when the event is resolved or at the end of the trial.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs**: The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE. Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.
- **SAEs fulfilling the MESI criteria:** In addition to above, the medication error form **within 14 calendar days** of the investigator's first knowledge of the AE.
- **SAEs fulfilling criteria for additional data collection:** In addition to above, the corresponding additional data collection form **within 14 calendar days** of investigators first knowledge of the event
- **Non-serious AE fulfilling the MESI criteria:** The AE form, safety information form and medication error form **within 14 calendar days** of the investigator's first knowledge of the event.
- **Non-serious AE fulfilling criteria for additional data collection:** The AE form, and additional data collection form **within 14 calendar days** of the investigators first knowledge of the event
- **AEs for adjudication:** Event Adjudication form should be completed by investigator **within 14 calendar days**. The investigator should provide the medical source documents within 30 days or as soon as possible and on an ongoing basis.

If the eCRF is unavailable, the concerned AE information must be reported on paper forms and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the appropriate forms in the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.

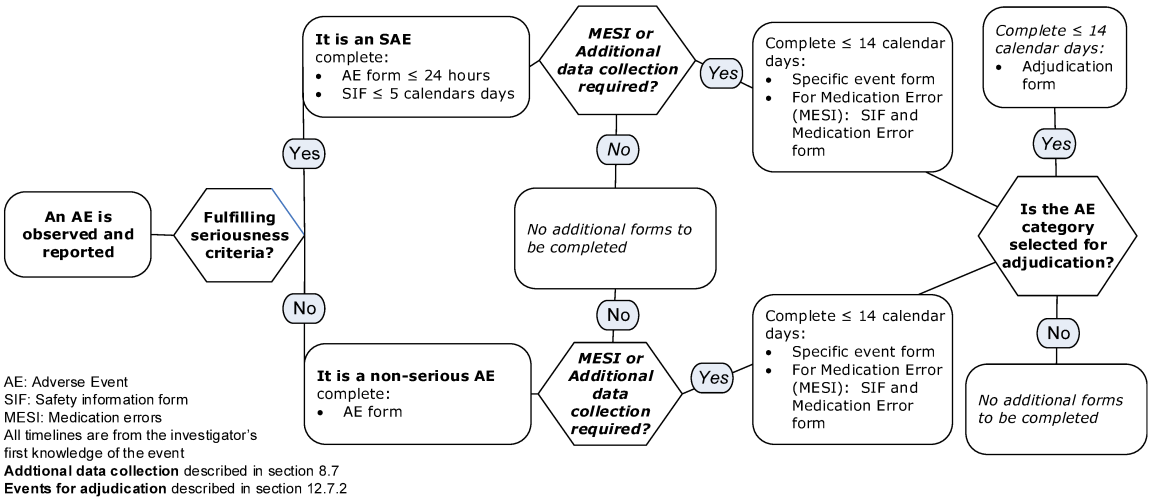


Figure 12–1 Initial reporting of adverse events

Reporting of trial product-related SUSARs by Novo Nordisk:
Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and GCP.[1] In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) of trial product-related SUSARs in accordance with local requirement and GCP,[1] unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication:
If a SAE and/or MESI is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this AE to relevant regulatory authorities.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.
Follow up information must be reported to Novo Nordisk according to the following:

- **SAEs**: All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved.

Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.
- **Non-serious AE fulfilling the MESI criteria or additional data collection criteria:** Non-serious AE fulfilling the MESI criteria or additional data collection criteria must be followed as specified for non-serious AEs. Follow-up information on MESIs or AEs with additional data collection should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria or the criteria for additional data collection.

The investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Dulaglutide, solution for injection, 0.75 mg/0.5 mL in a pre-filled pen
- Dulaglutide, solution for injection,1.5 mg/0.5 mL in a pre-filled pen
- Novo Nordisk needles for PDS290 pen-injector

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs, SAEs, and/or MESI.

Technical complaints must be reported on a separate technical complaint form. A technical complaint form for each batch or lot number or for each DUN must be completed.

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints within **5 calendar days**

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A print or copy of the technical complaint form must be sent with the sample.

The investigator must ensure that the technical complaint sample contains the batch or lot number and, if available, the DUN.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see section 9).

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who have received trial product(s). In case of pregnancy, the subject must discontinue from trial product, please see sections 6.5 and 8.1.6.

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age.

The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant.

The following must be collected and reported by the investigator to Novo Nordisk - electronically (e.g. in PDF format), or by fax or courier:

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

   When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

   Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. **Reporting of AE information**
   The investigator has to report AEs in connection with the pregnancy as well as in the foetus and newborn infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous abortion), and congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE.

Forms and timelines for reporting AEs:

Non-serious AEs:

- Paper AE form* **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

- Paper AE form* **within 24 hours** of the investigator's first knowledge of the SAE.
- Paper safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

* It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or newborn infant.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

Semaglutide: Events of nausea, vomiting and headache have been reported in connection with accidental administration of semaglutide doses up to 4 mg. No symptoms of hypoglycaemia have been reported in connection with overdose of semaglutide. In the event of overdosage, appropriate supportive treatment should be initiated according to subject’s clinical signs and symptoms

Dulaglutide: Overdoses have been reported in clinical studies. Effects associated with these overdoses were primarily mild or moderate gastrointestinal events (e.g., nausea, vomiting) and non-severe hypoglycaemia. In the event of overdose, appropriate supportive care (including frequent plasma glucose monitoring) should be initiated according to the subject’s clinical signs and symptoms.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal semaglutide safety committee to perform ongoing safety surveillance as well as surveillance of laboratory safety data. The semaglutide safety committee may recommend unblinding of any data from the NN9535 and NN9536 semaglutide for obesity programmes for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

12.7.2 Event adjudication committee

An independent external event adjudication committee (EAC) is established to perform qualitative or quantitative validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE. Pre-defined clinical data consist of copies of source documents collected and delivered by the trial sites.

The EAC is composed of permanent members covering required medical specialities. EAC members must disclose potential conflicts of interest and must be independent of Novo Nordisk.

The events are reviewed by the EAC in a blinded manner. The EAC will have no authorisations to impact on trial conduct, trial protocol or amendments.

The EAC works in accordance with written guidelines included in the EAC Charter describing in details the composition, tasks, responsibilities and work processes of the committee.

The events outlined in Table 12–2 have been selected for adjudication in order to obtain an external independent validation of the diagnosis. In addition, cardiovascular events are being adjudicated according to FDA requirements.

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (e.g. x-ray, ECGs, ultrasound images, discharge summaries, pathology reports and death certificates). The investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk or the Event Adjudication Vendor.

The assessments made by the EAC will be included in the clinical trial report as well as assessments made by the investigator. However, the adjudication made by an EAC, given its independence and in-depth analysis of each event, will be attributed with greater importance of the two. The outcome of adjudication will be kept in the clinical trial database.

The following AEs will be adjudicated in this trial:

Table 12–2 Adverse events for adjudication

Event	Definition
Fatal event	All cause mortality: • Cardiovascular death, • Non-cardiovascular death, • Undetermined cause of death
Acute coronary syndrome	All types of MI must be reported: • Spontaneous MI (including re-infarction and MI associated with stent thrombosis) • Percutaneous coronary intervention (PCI) related MI • Coronary artery bypass graft surgery (CABG) related MI • Silent MI All events with symptoms of myocardial ischaemia requiring hospitalisation must be reported.
Cerebrovascular event	TIA: TIA is defined as a transient (<24 hours) episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischaemia, without acute infarction. Stroke (ischaemic, haemorrhagic, undetermined) : Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction.
Heart failure requiring hospitalisation	Clinical manifestations of new episode or worsening of existing heart failure.
Pancreatitis	Two of following diagnostic criteria fulfilling the diagnosis of acute pancreatitis: • Severe acute abdominal pain • Elevated blood levels of pancreatic enzymes (lipase, amylase) > 3xUNR • Characteristic imaging finding (e.g. by ultrasound, CT, MRI) Chronic pancreatitis will be defined by characteristic imaging finding (e.g. by ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings
Thyroid diseases, if thyroid neoplasm or resulting in thyroidectomya	All thyroid diseases requiring thyroidectomy, including partial thyroidectomy (e.g. lobectomy, partial lobectomy and biopsies) will be adjudicated. All thyroid neoplasms will be adjudicated.
Malignant neoplasm	Malignant neoplasms, defined as neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems. Note: For operational reasons thyroid neoplasm will be reported as a thyroid disease.

All AEs will be screened for potential missed events for adjudication and if needed, the investigator will be asked to provide additional information such as an alternative aetiology, underlying cause(s) and/or clinical details.

The adjudication vendor or EAC can decide to have an AE adjudicated even if not initially reported as an event for adjudication by the investigator.

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures.

AEs for adjudication must be reported according to section 12.2. In addition, the specific adjudication document collection form should be completed within 14 calendar days of the investigator's first knowledge of the AE, and all relevant predefined documents provided according to instructions in the event adjudication site manual.

13 Case report forms

Novo Nordisk will provide a system for the eCRF. This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms

In addition paper AE forms, technical complaint forms and safety information forms will be provided. These must be used when access to the eCRF is revoked or if the eCRF is unavailable.

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the investigator's delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

The pregnancy forms are paper based CRFs. Also, the AE forms, technical complaint forms, and safety information forms will be provided in paper but are only to be used if for any reason the eCRF is unavailable.

The investigator must ensure that data is recorded in these forms as soon as possible after the visit.

At the end of the trial the investigator must ensure that all remaining data have been entered into the eCRF no later than 3 days after LPLV at the site in order to ensure the planned lock of the database.

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks for trial sites with active subjects (defined as subjects in screening, treatment or follow-up).

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

All data must be verifiable in source documentation other than the CRF.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The original diaries and PROs must not be removed from the trial site, unless they form part of the CRF and a copy is kept at the site.

The monitor will ensure that the eCRFs are completed and that paper CRFs are collected.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent
- Reason for screen failure

Monitors must review the subject's medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the CRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a contract research organisation.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

In cases where data management activities are delegated to external vendors, there will be regular transfers of data during the trial.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

17 Statistical considerations

General considerations

No interim analyses or other analyses of unmasked or between group data will be performed before the database is locked.

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

Data from all trial sites will be analysed and reported together.

If an assessment has been made both at screening and randomisation, and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If an assessment is missing at randomisation, but available at screening, then the screening value will be used as the baseline value.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

Results from a statistical analysis will be presented by the estimated treatment contrasts at week 40 with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference if not otherwise specified.

The two principal comparisons presented from a statistical analysis are

- s.c. semaglutide 0.5 mg versus dulaglutide 0.75 mg
- s.c. semaglutide 1.0 mg versus dulaglutide 1.5 mg

Primary estimand

The primary objective of the trial is to compare the effect of once-weekly dosing of two dose levels of s.c. semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of each of the two dose levels of s.c. dulaglutide (0.75 mg and 1.5 mg) on glycaemic control in subjects with T2D on a background treatment with metformin.

The primary estimand will be:

- de-jure treatment difference at week 40 for all randomised subjects if all subjects adhered to treatment and did not initiate antidiabetic rescue medication

This estimand assesses the glycaemic benefit a future subject is expected to achieve if he/she initiates and continue treatment with s.c. semaglutide as compared to dulaglutide. It is considered a

clinically relevant estimand as it provides information to treating clinicians about the expected glycaemic efficacy of s.c. semaglutide for purposes of treating individual subjects with T2D.

Missing data considerations

Since both semaglutide and dulaglutide are GLP-1 RA, it is reasonable to assume that missing data in both arms will be similar in timing, extent and reason. Based on the phase 2 semaglutide dose-finding trial (NN9535-1821) and the slower dose escalation implemented in this trial, the rate of discontinuing treatment prematurely or initiating rescue medication on top of trial product is expected to be maximum 25% and similar across treatment arms after 40 weeks of treatment.

Since efficacy for both semaglutide and dulaglutide have been shown, missing data due to ineffective therapy is not anticipated to be a notable issue. However, some missing data due to AEs is expected in both treatment arms because of gastrointestinal related AEs leading to premature treatment discontinuation primarily during initiation and dose escalation.

Descriptive summaries and graphical representation of extent, reason(s) for and pattern of missing data will be presented by treatment arm.

17.1 Sample size calculation

The primary endpoint is change from baseline in HbA_{1c} after 40 weeks of treatment. For HbA_{1c}, both non-inferiority and subsequently superiority are planned to be tested at each dose level (semaglutide 0.5 mg versus dulaglutide 0.75 mg and semaglutide 1.0 mg versus dulaglutide 1.5 mg). The confirmatory secondary endpoint is change from baseline in body weight after 40 weeks of treatment. For body weight, superiority is planned to be tested at each dose level.

The sample size calculation is based on jointly meeting four out of the six pre-specified confirmatory hypotheses shown in Figure 17–1. The closed testing procedure described in Bretz et al[39] is used to control the overall type-1 error at a nominal two-sided 5% level. The four hypotheses are:

- HbA_{1c} non-inferiority of semaglutide 0.5 mg versus dulaglutide 0.75 mg (margin of 0.4%)
- Body weight superiority of semaglutide 0.5 mg versus dulaglutide 0.75 mg
- HbA_{1c} non-inferiority of semaglutide 1.0 mg versus dulaglutide 1.5 mg (margin of 0.4%)
- Body weight superiority of semaglutide 1.0 mg versus dulaglutide 1.5 mg

The sample size is calculated using the calcPower function in the R package, gMCP[40] using 10000 simulations. All of the six pre-specified confirmatory hypotheses are assumed to be independent. Since positive correlations are expected, the assumption of independence is viewed as conservative.

Furthermore, the sample size calculation is based on the following assumptions:

Based on the phase 2 s.c. semaglutide dose-finding trial (NN9535-1821), the standard deviation for HbA_{1c} is assumed to be 1.1% and the standard deviation for body weight is assumed to be 4 kg.

The assumed treatment difference in HbA_{1c} of semaglutide relative to dulaglutide at week 40 within both dose levels is zero. The assumed treatment difference in body weight of semaglutide relative to dulaglutide at week 40 within both dose levels is 1.5 kg. A 50% smaller effect on body weight is assumed in the 25% of subjects expected to discontinue treatment prematurely or initiate rescue medication on top of trial product. This leads to an adjusted treatment effect of 1.35 kg for body weight, which is the value used in the sample size calculation. Based on oral semaglutide phase 2 results (NN9924-3790), the 50% efficacy retention is viewed as conservative in light of the primary analysis but less so for the in-trial sensitivity analyses that uses all data collected during the trial.

With the above assumptions, allocating 299 subjects to each of the semaglutide and dulaglutide arms yields 90% power to confirm HbA_{1c} non-inferiority and body weight superiority between semaglutide and dulaglutide at both dose levels.

Calculated powers for selected individual hypotheses are presented in Table 17–1. In total 4×299 = 1196 subjects are planned to be randomised.

Table 17–1 Calculated powers for individual hypotheses

Statistical test	HbA_{1c} non-inferiority (margin=0.40%)		Body weight superiority		HbA_{1c} superiority	
Treatment dose level	High	Low	High	Low	High	Low
Power (%)	99	99	95	95	1.2	1.2

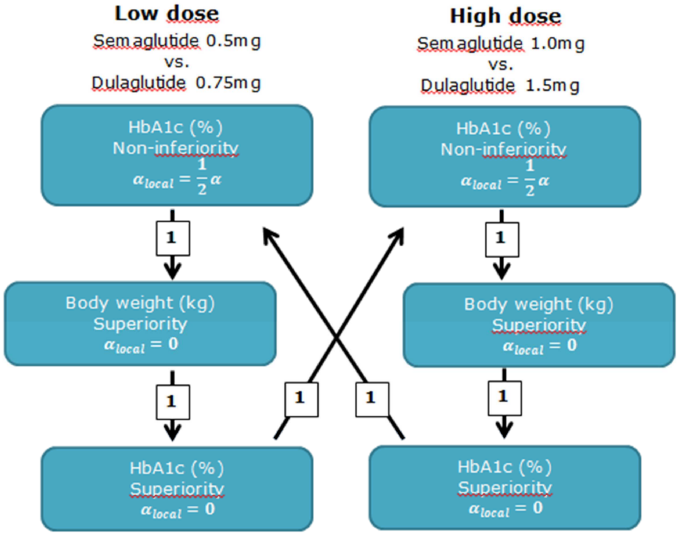


Figure 17–1 Graphical illustration of the closed testing procedure

The Type-I error for the six pre-specified confirmatory hypotheses will be controlled in the strong sense using the closed testing procedure in Figure 17–1. The initial allocation of the overall significance level of α=0.05 (two-sided) is split equally between non-inferiority at the two dose levels. The local significance level (α_{local}) will be reallocated if a hypothesis is confirmed according to the weight given by directed edge between nodes (the hypotheses).

17.2 Definition of analysis sets

The following analysis sets will be defined:

Full analysis set (FAS): includes all randomised subjects exposed to at least one dose of trial product. Subjects in the FAS will contribute to the evaluation "as randomised".

Safety analysis set (SAS): includes all randomised subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation "as treated".

Per protocol (PP) analysis set: includes all subjects in the FAS who fulfil the following criteria:

- Have not violated any inclusion criteria
- Have not fulfilled any exclusion criteria
- Have a non-missing HbA_{1c} measurement at screening and/or randomisation
- Is on trial product at week 28 and have at least one non-missing HbA_{1c} measurement at or after week 28

Subjects in the PP analysis set will contribute to the analysis "as treated".

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion will be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

Data selections and observations periods

Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial, which is until the follow-up phone contact (P10).

The data to be used in all analyses will be selected in two steps.

Step 1: The subjects and treatment principle (as treated or as randomised) to be used in the analysis will be selected based on the specified *analysis set.*

Step 2: Data points for subjects used in the analysis set will be selected according to whether or not the data points belongs to the specified *observation period* (In-trial, on-treatment or on-treatment without rescue as defined below). Information collected with onset date outside the observation period will be treated as missing and therefore excluded from the corresponding analysis. For adjudicated events, onset date will be the EAC adjudicated onset date.

- ***In-trial:*** The in-trial observation period includes observations recorded at or after randomisation (as registered in IWRS) and not after the last subject-investigator contact, which is scheduled to take place 5 weeks after planned last dose of trial product at a follow-up phone contact (P10). For subjects who withdraw their informed consent, the in-trial observation period ends at their date of withdrawal. In the case a subject dies during the trial, the date of death will be the end-date of the in-trial observation period. If a subject is lost to follow-up, the end of his/her in-trial period is defined as the date of the last subject-investigator contact (site or phone visit). Analysis based on this observation period includes data regardless of treatment exposure and/or usage of non-investigational antidiabetic medications. Since non-investigational antidiabetic medications can mask or exaggerate both the efficacy and safety effects, this observation period will be in line with the primary estimand and is considered supportive for both efficacy and safety evaluations.
- ***On-treatment:*** This observation period represents the time period where subjects are considered treated with trial product. The observation period is a subset of the in-trial observation period and two slightly different data handling rules will be needed to cover all assessments appropriately. For adjudicated events, ECGs and AEs including hypoglycaemic episodes, this observation period will represent information collected while subjects are

considered exposed to trial product. This corresponds to information collected up until the follow-up phone contact, which is scheduled to take place 5 weeks after premature treatment discontinuation to reflect five half-lives of s.c. semaglutide including a visit window of +7 days. For the remaining safety and efficacy assessments that are collected up until and not after the end of treatment visit, the follow-up period will not be included in the on-treatment observation period. In line with the primary estimand, the on-treatment observation period will be the primary observation period used in safety evaluations and considered supportive of efficacy evaluations.

- ***On-treatment without rescue:*** This observation period is a subset of the on-treatment observation period, where subjects do not receive any non-investigational antidiabetic medication (rescue medication). Specifically it includes observations recorded at or after date of first dose of trial product and not after the first occurrence of the following:
    - The last dose of trial product plus the dosing interval
    - Initiation of rescue medication

For subjects who have no post-baseline scheduled assessments available in the on-treatment without rescue period, the baseline value will be carried forward to the first scheduled visit for the associated endpoint to ensure that all randomised subjects will contribute to the statistical analysis. In line with the primary estimand, the on-treatment without rescue observation period will be the primary observation period used in efficacy evaluations.

17.3 Primary endpoint

The primary analysis used to estimate the primary estimand will be based on FAS using data from the on-treatment without rescue observation period in a Mixed Model for Repeated Measures (MMRM). A restricted maximum likelihood (REML) will be used. The model will include all post baseline HbA_{1c} measurements collected at scheduled visits up to and including week 40 data as dependent variables. The independent effects included in the model will be treatment and country as fixed effects and baseline response as covariate, all nested within visit. An unstructured covariance matrix will be employed for measurements within the same subject, assuming that measurements across subjects are independent. From this model, the two by dose level estimated treatment differences between s.c. semaglutide versus dulaglutide at week 40 will be presented together with associated two-sided 95% confidence intervals and unadjusted two sided p-values (nominal alpha=0.05) for testing non-inferiority and superiority.

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. This analysis assumes that the missing data mechanism is missing at random (MAR). Thus, for a subject who has missing data, MAR assumes a value for the endpoint based on observed data of subjects whose baseline explanatory variables and response up to withdrawal are similar to that of the discontinued subject. Since there is no historical evidence suggesting that subjects

discontinuing semaglutide prematurely have better outcome on average than those who remain on treatment, the primary analysis is not expected to bias the estimated HbA_{1c} treatment effect for the primary estimand in favour of semaglutide to any important degree. This is based on the s.c. semaglutide phase 2 (NN9535-1821) results and further supported by data from liraglutide clinical trials.

Hypotheses tested for the primary endpoint

For HbA_{1c}, the following two confirmatory hypotheses are planned to be tested at each dose level comparing; (i) semaglutide 0.5 mg versus dulaglutide 0.75 mg and (ii) semaglutide 1.0 mg versus dulaglutide 1.5 mg with mean treatment difference defined as μ=(semaglutide minus dulaglutide):

- Non-inferiority using a non-inferiority margin of 0.4
  - H_0: μ>=0.4% against Ha: μ <0.4%

- Superiority
  - H_0: μ>=0.0% against Ha: μ<0.0%

Operationally, the hypotheses will be assessed using two-sided p-values.

Multiplicity and criteria for confirming hypotheses

The Type-I error for testing the six confirmatory hypotheses related to HbA_{1c} and body weight endpoints will be preserved in the strong sense at 5% (two-sided) using the weighted Bonferroni-based closed testing procedure described in Bretz et al[39] and outlined in Figure 17–1. First the 2 non-inferiority hypotheses at each dose level will be tested each at its initial allocated local significance level of 0.025%. If a non-inferiority hypothesis is confirmed, the local significance level will be reallocated according to the edge going out of the confirmed hypothesis as specified in Figure 17–1. Each of the following hypotheses will be tested at their local significance level (α-local). This process will be repeated until no further hypothesis can be confirmed.

Non-inferiority and/or superiority will be considered confirmed if the mean treatment difference is supporting the corresponding hypothesis and the two-sided p-value (nominal alpha=0.05) is strictly below its local two-sided significance level as defined by the closed testing procedure in Figure 17–1. This is equivalent to using a one-sided p-value (nominal alpha=0.025) and a one-sided 2.5% overall significance level in the closed testing procedure.

Sensitivity analyses

The aim of the below pre-specified sensitivity analyses is to explore the impact of departures from the missing data assumption made in the primary analysis of HbA_{1c} and the confirmatory secondary analysis of body weight (see section 17.4.1). This is consistent with European Medicines Agency (EMA) recommendations[41] and with a report from the US National Research Council.[42] Since

conservatism (i.e. avoiding bias in favour of semaglutide) depends on the context, the sensitivity analyses are targeted to whether non-inferiority or superiority is being tested.

Pattern-mixture model using multiple imputation addressing both non-inferiority and superiority
The below pattern-mixture model based sensitivity analyses imputes missing data in a way that is likely to be less favourable for s.c. semaglutide as compared to the primary HbA_{1c} analysis. The multiple imputation sensitivity analysis stress-tests the primary HbA_{1c} conclusions by changing the missing data assumptions about s.c. semaglutide, while using the MAR assumption for subjects randomised to dulaglutide.

- *Comparator multiple imputation analysis* - In this analysis, all monotone missing data for subjects randomised to s.c. semaglutide 1.0 mg are imputed to have HbA_{1c} response trajectory statistically similar to subjects treated with dulaglutide 1.5 mg and for subjects randomised to s.c. semaglutide 0.5 mg are imputed to resemble in distribution subjects treated with dulaglutide 0.75 mg. The analysis will be based on the FAS using the on-treatment without rescue observation period. A sequential multiple imputation modelling approach by dose level will be implemented in which all observed post-baseline dulaglutide data are used to impute all monotone missing values. As a preliminary step, non-monotone or intermediate missing data will be imputed by treatment using a Markov Chain Monte Carlo method under the assumption of MAR and a multivariate normal distribution over baseline and scheduled post baseline measurements. For non-inferiority testing an additional step is included. Here all the imputed values in a s.c. semaglutide treatment arm are made worse by the non-inferiority margin at week 40. This is based on the assumption that missing values for subjects randomised to s.c. semaglutide will be imputed according to a treatment expected inferior to dulaglutide in order to ensure that non-inferiority is not unduly favoured.

Sensitivity analyses addressing non-inferiority
In support of non-inferiority testing, the below two sensitivity analyses will be performed. These sensitivity analyses only include a subset of all randomised subjects so the integrity of randomisation may not be maintained. Therefore, while the below two analyses generally are conservative for testing non-inferiority, the inherent risk for bias in any direction cannot be excluded.

- *PP analysis* – the statistical analysis will be the same as the primary MMRM based analysis but it will be based on the PP analysis set and the on-treatment without rescue observation period.
- *Complete case analysis* – includes subjects in the FAS who do not have their endpoint imputed in the primary analysis. The change from baseline in HbA_{1c} at week 40 will be analysed by a linear normal model (analysis of covariance (ANCOVA)) with treatment and country as fixed effects and baseline HbA_{1c} as a covariate.

Other sensitivity analyses

The following secondary estimand will be defined:

- de-facto treatment difference at week 40 for all randomised subjects

This estimand assesses the average effect in a future population that results from treatment with s.c. semaglutide plus antidiabetic rescue medication(s) as compared to treatment with dulaglutide plus antidiabetic rescue medication(s). Interpretation of this estimand depends on whether the use of antidiabetic rescue medication and treatment adherence in this trial reflects clinical practice. The de-facto estimand will be estimated from the below analysis:

- *In-trial analysis* – This analysis will be based on the FAS using the in-trial observation period. The statistical analysis will be the same as the primary MMRM based analysis. The MAR assumption is considered a reasonable approach for handling missing data, as the two trial products can be considered to have efficacy similar to standard of care treatment available for treatment of T2D. This analysis will also be considered as a sensitivity analysis for evaluating the robustness of the primary analysis.

The last sensitivity analysis will be:

- *Last observation carried forward (LOCF) analysis* – This analysis will be based on the FAS using the on-treatment without rescue observation period with missing data imputed by LOCF. Based on the complete data set, the change from baseline in HbA_{1c} at week 40 will be analysed by a linear normal model (ANCOVA) with treatment and country as fixed effects and baseline HbA_{1c} as a covariate.

Assessment of sensitivity analyses

The results from the sensitivity analysis will be collectively used to interpret the confirmatory trial conclusions on HbA_{1c} and body weight, and in particular evaluate the impact of the MAR assumptions. No absolute criteria will be defined as to when a sensitivity analysis can be defined to have confirmed the robustness of the conclusions. Due to the large number of the sensitivity analyses and their inherent conservative nature, it is not considered a requirement that all confirmatory hypotheses are confirmed across all the sensitivity analyses. The results of the sensitivity analysis will be discussed in the clinical trial report with the aim to use the sensitivity results in totality to evaluate the credibility of the confirmatory trial conclusions.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoint

The confirmatory secondary endpoint is change from baseline to week 40 in body weight (kg). This endpoint will be analysed in the same type of model as the primary endpoint, except with baseline body weight as a covariate instead of baseline HbA_{1c}. From this model the two by dose level estimated treatment differences between semaglutide versus dulaglutide will be presented at week 40 together with associated two-sided 95% confidence intervals and unadjusted two sided p-values (nominal alpha=0.05). The same sensitivity analyses as pre-specified for testing superiority for the primary HbA_{1c} endpoint will also be performed to evaluate the robustness of the body weight superiority conclusions.

Confirmatory secondary hypothesis
For body weight, the following confirmatory hypothesis will be tested at each dose level comparing; (i) semaglutide 0.5 mg versus dulaglutide 0.75 mg and (ii) semaglutide 1.0 mg versus dulaglutide 1.5 mg with mean treatment difference defined as μ=(semaglutide minus dulaglutide):

- Superiority
  - H_0: μ >=0.0% against Ha: μ <0.0%

Superiority will be considered confirmed if the corresponding two-sided p-value (nominal alpha=0.05) is strictly below its local two-sided significance level as defined by the closed testing procedure in Figure 17–1.

17.4.2 Supportive secondary endpoints

17.4.2.1 Efficacy endpoints

The supportive secondary efficacy endpoints will be presented based on FAS using the on-treatment without rescue observation period as the key observation period with the in-trial observation period being supportive.

Endpoints include change from baseline to week 40 in:

- FPG*
- SMPG, 7-point profile:
  - Mean 7-point profile, defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time
  - Mean post prandial increment (over all meals)

- Fasting blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)
- BMI and waist circumference
- Systolic and diastolic blood pressure*
- Patient reported outcomes
  - SF-36v2™
  - DTSQ*

The above continuous endpoints will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as a covariate. Fasting blood lipids profile endpoints will be log-transformed prior to analysis including also the relevant log-transformed baseline value used as a covariate.

Subjects who after 40 weeks treatment achieve (yes/no)

- HbA_{1c} <7.0% (53 mmol/mol) ADA target
- HbA_{1c} ≤6.5% (48 mmol/mol) AACE target*
- Weight loss ≥5%
- Weight loss ≥10%
- HbA_{1c} <7.0% (53 mmol/mol) without severe or BG confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA_{1c} reduction ≥1%
- Weight loss ≥3%
- HbA_{1c} reduction ≥1% and weight loss ≥3%

The above eight binary endpoints will be analysed using a logistic regression model with treatment and region as fixed effects and baseline response as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c} endpoints, baseline weight for weight endpoints and both baseline HbA_{1c} and baseline weight for the binary endpoint that combines both parameters). To account for missing data, the analysis will be made using a sequential multiple imputation approach as described below:

- Multiple imputed data sets (100) will be created in which missing values for the underlying continuous assessments are imputed by treatment group assuming MAR and as described in section 17.3.
- The binary endpoint will be created for each of the 100 complete data sets
- Each of the created complete data set will be analysed with the logistic model and inference will be drawn using Rubin's rule.[43]

PRO outcomes

The PRO outcomes endpoints that will be analysed at week 40 are:

- PRO questionnaire outcome DTSQs (individual items and treatment satisfaction score (6 of the 8 items summed)), and
- PRO questionnaire outcome SF-36v2™

The above continuous endpoints will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as a covariate.

7-point profile (SMPG)

Subjects will be asked to perform SMPG measurements before and 90 minutes after breakfast, lunch, dinner, respectively, and at bedtime.

The endpoints from the 7-point profiles that will be analysed at week 40 are:

- Mean of the 7-point profile, defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time
- Mean increment over all meals

The mean of the 7-point profile and the mean of the post prandial increments at week 40 will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as a covariate.

17.4.2.2 Safety endpoints

All safety endpoints will be evaluated based on SAS and the on-treatment observation period as the primary observation period with the in-trial observation period being supportive if not otherwise specified.

The following endpoints are used to support the safety objectives:

- Number of TEAEs
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemia episodes
- Treatment emergent severe or BG confirmed symptomatic hypoglycaemia (yes/no)

Change from baseline to week 40 in:

- Lipase
- Amylase
- Pulse

The above continuous endpoints will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as covariate. Lipase and amylase endpoints will be log-transformed prior to analysis including also the relevant log-transformed baseline value as covariate.

The following laboratory assessments will be summarised descriptively:

- Haematology
- Biochemistry
- Calcitonin

The following categorical safety evaluations will be summarised descriptively:

- ECG category
- Physical examination

Calcitonin

In addition to the continuous summaries, calcitonin will be displayed in terms of the number of subjects (N), the percentage of subjects (%) and the event rate per 100 years of exposure (R). The below criteria are defined for categorical tabulations. Summaries will be presented for all subjects and by gender.

- Persistent (all post baseline measurements)
- From < upper normal limit (UNL) to persistently ≥ UNL
- From <UNL to persistently ≥1.5 UNL
- From <UNL to persistently ≥20 ng/L
- From <UNL to persistently ≥50 ng/L
- From <20 ng/L to persistently ≥20 ng/L
- From <50 ng/L to persistently ≥50 ng/L

Adverse Events

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

A TEAE is defined as an AE with onset in the on-treatment period (see definition of observation period in section 17.2).

TEAEs will be summarised in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 patient years of observation time (R) for the on-treatment observation period. Supportive summaries of AEs will be made for the in-trial observation period.

Classification of Hypoglycaemia:

Hypoglycaemic episodes will be summarised for the SAS and the on-treatment observation period. No supportive summaries will be made based on the in-trial observation period and episodes with onset date after the on-treatment observation period will be reported in listings only.

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset is in the on-treatment period (see definition of observation period in section 17.2)

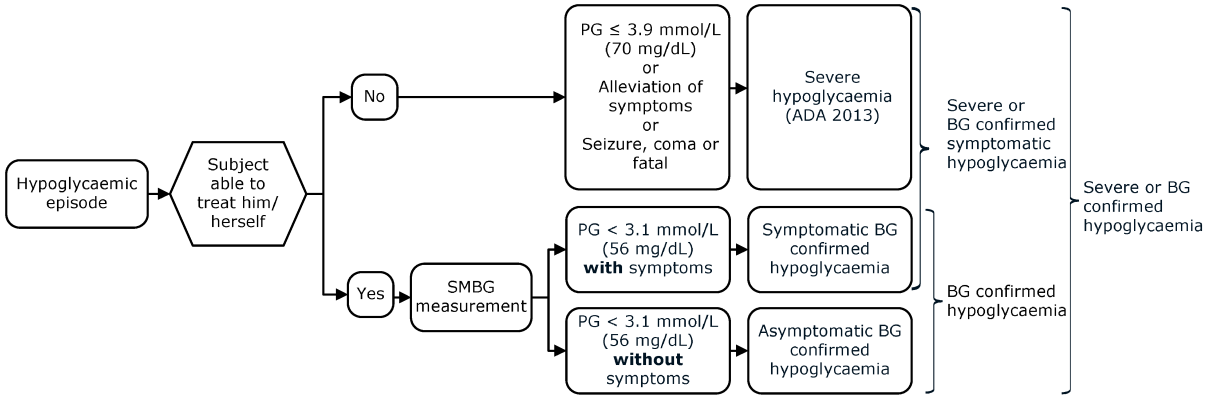
Nocturnal hypoglycaemic episodes: are episodes occurring between 00:01 and 05.59 both inclusive.

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–2) and the ADA classification of hypoglycaemia (see Figure 17–3).

Novo Nordisk classification of hypoglycaemia
In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL).[44] Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 17–2) in addition to the ADA classification:

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[36] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–2 Novo Nordisk classification of hypoglycaemia

ADA classification[36] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

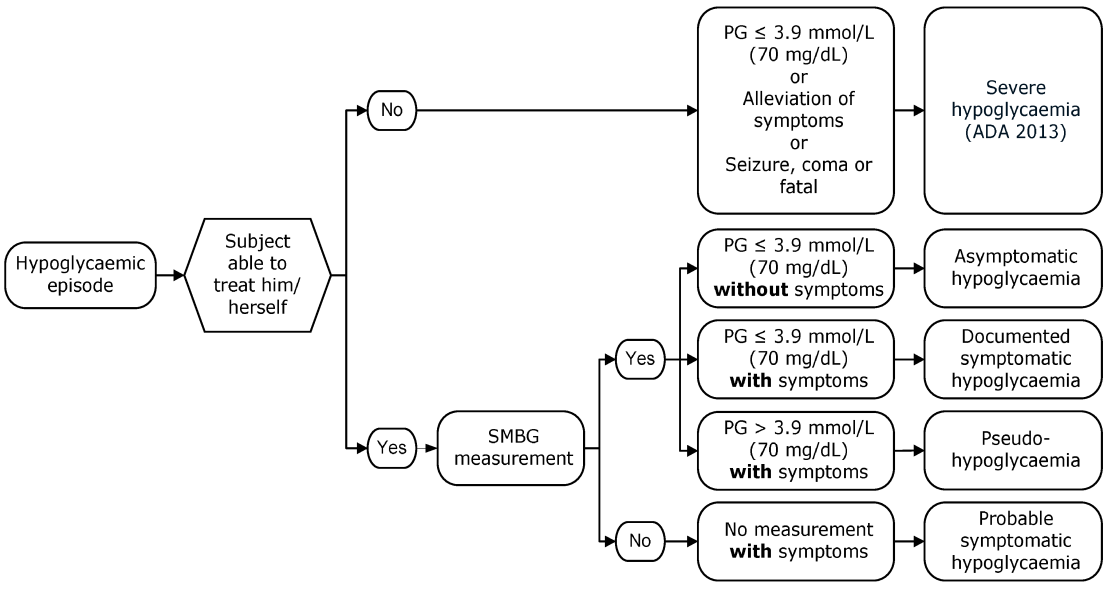


Figure 17–3 ADA classification of hypoglycaemia

Data on treatment emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one episode, the percentage of subjects with at least one episode (%), the total number of episodes and the episode rate per 100 years of exposure. Summaries of treatment emergent hypoglycaemic episodes will be presented as an overview including all episodes and episodes by severity.

Number of severe or BG confirmed symptomatic hypoglycaemic episodes

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period covered by the subject's on-treatment observation period as offset. The model will include factors for treatment and region as fixed factors and baseline HbA_{1c} as covariate.

Severe or BG confirmed symptomatic hypoglycaemic episodes (yes/no)

The binary endpoint indicating whether a subject has at least one treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using a logistic regression model with treatment and region as fixed factors and baseline HbA_{1c} as covariate.

17.5 Health economics and/or patient reported outcomes

The PRO questionnaires, SF-36v2™ and DTSQs, derived endpoints for overall scores and domains will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as covariate.

18 Ethics

18.1 Benefit-risk assessment of the trial

18.1.1 Risks and precautions

18.1.1.1 Semaglutide

The nonclinical safety programme of semaglutide has not revealed any identified safety issues for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity. See section 3.1.4.

The sections below describe identified and potential risks associated with semaglutide treatment, based on findings with other GLP-1 RAs and observations in nonclinical and clinical trials with semaglutide administered s.c. once-weekly. For each of these risks, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

Thyroid C-cell tumour

The human relevance of the proliferative C-cell changes found in rodents is unknown, but data suggest that rodents are more sensitive to the mode of action of GLP-1 RAs for induction of C-cell tumours with GLP-1 RAs. Recently published data have shown that the GLP-1 receptor is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor mediated C-cell changes in humans is considered to be low.[25] However, as a precaution, subjects with a family or personal history of Multiple Endocrine Neoplasia Type 2, familial Medullary Thyroid Carcinoma, personal history of non-familial Medullary Thyroid Carcinoma, and subjects with a screening calcitonin ≥50 ng/L will be excluded from the trial. During the trial, calcitonin will be measured on a regular basis and guidance for investigators of further evaluation and action on elevated calcitonin concentrations will be carried out. This will ensure appropriate and consistent handling of elevated calcitonin levels across trials.

Teratogenicity (nonclinical embryo-foetal toxicity)

Semaglutide has been concluded teratogenic in rats. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function. As the yolk sac does not play such a role for nutrition of the embryo in humans, this effect is not considered relevant for humans. However, as a precaution, subjects fulfilling the following exclusion criteria will be excluded: female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive methods throughout the trial including the 5 week follow-up period (adequate contraceptive measures as required by local regulation or practice).

Gastrointestinal adverse events

Consistent with findings from other GLP-1 RAs, the most frequently reported AEs in the clinical trials with semaglutide thus far have been gastrointestinal disorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). In the completed trial (NN9535-3819) a slower dose-escalation regimen was used compared to previous trials, and this substantially improved the gastrointestinal tolerability profile. Therefore, a 4-week dose escalation regimen has been developed and is used in the ongoing clinical phase 3 programme for semaglutide administered s.c. once-weekly.

Allergic reactions and injection site reactions

As is the case with all protein based pharmaceuticals, subjects treated with semaglutide risk developing immunogenic and allergic reactions. These may include localised injection site reactions or generalised reactions including urticaria, rash or pruritus. Severe allergic reactions such as anaphylactic reactions could potentially also pose a risk for subjects treated with semaglutide.

Hypoglycaemia

Based on current knowledge about the GLP-1 RA drug class, there is a risk of hypoglycaemic episodes. Hypoglycaemic episodes have mainly been observed when a GLP-1 RA is combined with sulfonylurea or insulin. The risk for development of hypoglycaemia specifically with semaglutide in combination with sulfonylurea and insulin is unknown due to limited data.

Altered renal function

- Untoward effects of volume depletion, resulting from nausea, vomiting and dehydration, such as acute renal failure have been observed in subjects treated with GLP-1 RAs including semaglutide. Impaired renal function may increase the risk of metformin associated lactic acidosis when GLP-1 RAs are co-administered with metformin. As a precaution serum creatinine is measured regularly. In subjects treated with metformin who experience prolonged or severe nausea and vomiting, the investigator should monitor serum creatinine, and if clinically indicated, withhold metformin until resolution of the renal dysfunction.

Acute pancreatitis

- Acute pancreatitis, including reports of severe necrotising and haemorrhagic forms, has been associated with GLP-1 RAs. However, data from observational studies suggest an increased frequency of pancreatitis among diabetics and a relationship between pancreatitis and GLP-1 RAs can neither be established nor excluded.[45,46] As a precaution subjects with a history of acute or chronic pancreatitis will be excluded from the trial. Subjects will be monitored for elevated levels of amylase and lipase and be informed of the characteristic symptoms of acute pancreatitis.

Pancreatic cancer

- There is currently no support from non-clinical or clinical trials or post-marketing data that GLP-1-based therapies increase the risk of pancreatic cancer. However, as the long-term effects of stimulation of β-cells and suppression of α-cells are largely unknown, pancreatic cancer is considered a potential risk by the European Medicine Agency (EMA).

18.1.1.2 Dulaglutide

Being a GLP-1 RA dulaglutide shares many of the same potential risks for the subject as semaglutide. Please consult the EU SmPC,[28] US prescribing information[29] and the local prescribing information (non-US and non-EU countries) for dulaglutide (Trulicity®) for the following information on warnings and precautions/risks gathered under clinical trials and from post marketing data: thyroid C-cell tumours, acute pancreatitis, hypoglycaemia, hypersensitivity, severe gastrointestinal disease.

18.1.1.3 General precautions

All subjects will be included after a thorough evaluation in regards to in- and exclusion criteria defined in order to ensure that subjects are eligible for trial treatment. There are strict glycaemic rescue criteria in place to ensure acceptable glycaemic control at all times during the trial. It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2014 Standards of Medical Care in Diabetes.[47]

18.1.2 Benefits

In this trial subjects will be randomised to one of four treatment arms involving a treatment regimen anticipated to be more efficacious than the treatment they receive at the time of entry into the trial. Semaglutide has in a phase 2 trial (NN9535-1821) proven to have a clinical meaningful and dose-dependent effect on HbA_{1c}, FPG and body weight. Doses ≥0.8 mg weekly brought more subjects to target with regards to HbA_{1c} and FPG, and provided a greater weight loss than liraglutide 1.8 mg daily. Dulaglutide has shown non-inferiority on glycaemic control versus liraglutide and the drug has already been approved for the use in subjects with T2D.

It is expected that all subjects will benefit from participation through close contact with the trial site, with close follow-up of their diabetes, and a careful medical examination; all of which will most likely result in an intensified management of their diabetes.

All subjects in this trial will receive trial drug and auxiliary supplies free of charge.

18.1.3 Risk and benefit conclusion

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile of semaglutide generated from the clinical and nonclinical development

programme has not revealed any safety issues that would prohibit administration of once-weekly doses in accordance with the planned clinical trial. Dulaglutide is already a marketed drug approved for the use in subjects with T2D. It is concluded that the risk to the subjects in this trial is low and acceptable in view of the benefits a long-acting GLP-1 RA would provide to subjects with T2D.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[1] and the requirements in the Declaration of Helsinki.[2]

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand.

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the investigator must inform the subject in a timely manner, and a revised written subject information must be provided and a new informed consent must be obtained.

18.3 Data handling

If the subject is withdrawn from the trial or lost to follow up, then the subject's data will be handled as follows:

- Data already collected and data collected at the end-of-trial visit will be retained by Novo Nordisk, entered into the database and used for the trial report.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to subject during trial

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject by discretion of the investigator. The subject may receive a “welcome to the trial letter” and a “thank you for your participation letter” after completion of the trial. Further the subject may receive letters during the trial.

All written information to subjects must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have participated in the trial. If it has an impact, the actions needed to inform and protect the subjects should be described.

19 Protocol compliance

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the clinical database.

Documentation on protocol deviations must be kept in the investigator's trial master file and sponsor trial master file.

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

Before a trial site is allowed to start screening subjects, the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of IB and local label of comparator
- Signed and dated Agreement on Protocol
- Signed and dated agreement on protocol amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

- For US trial sites: verification under disclosures per Code of Federal Regulations of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the Investigational New Drug Application (IND)
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

By signing the protocol, each investigator agrees to comply fully with ICH GCP,[1] applicable regulatory requirements and the Declaration of Helsinki.[2]

By signing the protocol, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator must ensure adequate supervision of the conduct of the trial at the trial site.

The investigator will follow instructions from Novo Nordisk when processing data.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents including the subject identification code list should be kept in a secure locked facility, so no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

23 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial.

One (or more) investigator(s) will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator(s)) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications.[48]

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.[49]

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

Where required by the journal, the investigator from each trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[48] (sometimes referred to as the Vancouver Criteria).

Novo Nordisk will appoint investigator(s) to prepare publications in collaboration with Novo Nordisk.

23.1.2 Site-specific publication(s) by investigator(s)

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database. Individual investigators will have their own research subjects' data, and will be provided with the randomisation code after results are available.

24 Retention of clinical trial documentation

24.1 Retention of clinical trial documentation

Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

The files from the trial site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

26 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence, or any other liability of the sites or investigators conducting the trial, or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with:

Germany: German Drug Law dated August 24, 1976, last amended by article 3 of the law dated December 17, 2014 (Federal Law Gazette I p. 2222).

France: The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research."

27 References

1 International Conference on Harmonisation. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1), Step 4. 10 Jun 1996.

2 World Medical Association. Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. 1 Oct 2013.

3 DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am 2004; 88(4):787-835, ix.

4 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131):837-853.

5 Chuang LM, Tsai ST, Huang BY, Tai TY, Diabcare A. The status of diabetes control in Asia--a cross-sectional survey of 24 317 patients with diabetes mellitus in 1998. Diabet Med 2002; 19(12):978-985.

6 Ford ES, Li C, Little RR, Mokdad AH. Trends in A1C concentrations among U.S. adults with diagnosed diabetes from 1999 to 2004. Diabetes Care 2008; 31(1):102-104.

7 Holst JJ, Vilsbøll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. Mol Cell Endocrinol 2009; 297:127-136.

8 Kieffer TJ, Habener JL. The glucagon-like peptides. Endocr Rev 1999; 20(6):876-913.

9 Hare KJ, Vilsbøll T, Holst JJ, Knop FK. Inappropriate glucagon response after oral compared with isoglycemic intravenous glucose administration in patients with type 1 diabetes. Am J Physiol Endocrinol Metab 2010; 298:E832-E837.

10 Nauck MA. Incretin based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. Am J Med 2011; 124 (1 Suppl):S3-S18.

11 Flint A, Kapitza C, Hindsberger C, Zdravkovic M. The once-daily human glucagon-like peptide-1 (GLP-1) analog liraglutide improves postprandial glucose levels in type 2 diabetes patients. Adv Ther 2011; 28(3):213-226.

12 Kapitza C, Flint A, Hindsberger C, Zdravkovic M. The effect of the once-daily human GLP-1 analogue liraglutide on the pharmacokinetics of paracetamol. Diabetes 2008; 57(Suppl. 1):A593.

13 Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest 1998; 101(3):515-520.

14 Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsboll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. J Clin Endocrinol Metab 2011; 96(3):737-745.

15 Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia 1986; 29(1):46-52.

16 Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? Diabetologia 2011; 54:10-18.

17 Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. J Clin Invest 1967; 46(12):1954-1962.

18 Højberg PV, Vilsbøll T, Rabøl R, Knop FK, Bache M, Krarup T et al. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. Diabetologia 2009; 52:199-207.

19 Holst JJ. Enteroglucagon. Annu Rev Physiol 1997; 59:257-271.

20 Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia 1993; 36(8):741-744.

21 Toft-Nielsen MB, Madsbad S, Holst JJ. Determinants of the effectiveness of glucagon-like peptide-1 in type 2 diabetes. J Clin Endocrinol Metab 2001; 86(8):3853-3860.

22 Hansen L, Deacon CF, Orskov C, Holst JJ. Glucagon-like peptide-1-(7-36)amide is transformed to glucagon-like peptide-1-(9-36)amide by dipeptidyl peptidase IV in the capillaries supplying the L cells of the porcine intestine. Endocrinology 1999; 140(11):5356-5363.

23 Larsen J, Hylleberg B, Ng K, Damsbo P. Glucagon-like peptide-1 infusion must be maintained for 24 h/day to obtain acceptable glycemia in type 2 diabetic patients who are poorly controlled on sulphonylurea treatment. Diabetes Care 2001; 24(8):1416-1421.

24 ICH. ICH Harmonised Tripartite Guideline M3(R2): Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2). 11 Jun 2009.

25 Waser B, Blank A, Karamitopoulou E, Perren A, Reubi JC. Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas. Modern Pathology (2015) 28, 391–402; doi:10.1038/modpathol.2014.113; published online 12 Sep 2014

26 Investigators Brochure for s.c. Semaglutide (NN9535), Edition 10 or any updates hereof. 2015.

27 Dungan KM, Povedano ST, Forst T, Gonzalez JG, Atisso C, Sealls W et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet 2014; doi:10.1016/S0140-6736(14)60976-4:Early Online Publication, 11 July.

28 EU SmPC for Dulaglutide. 2014.

29 Trulicity (dulaglutide), USPI. Eli Lilly and Company. 2014.

30 Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012; 35(6):1364-1379.

31 Novo Nordisk. http://www.novonordisk-trials.com/website/content/how-we-disclose-trial-information.aspx. 2015.

32 De Angelius C., Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R et al. Clinical Trial Registration: A statement from the International Committee of Medical Journal Editors. N Engl J Med 2004; 351:1250-1251.

33 Food and Drug Administration Amendments Act of 2007. 11 Oct 2007.

34 The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, article 11. Official Journal of the European Communities May 2001.

35 The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. Official Journal of the European Communities April 2001.

36 Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013; 36(5):1384-1395.

37 McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. Diabet Med 2001; 18(9):690-705.

38 The rules governing medicinal products in the European Union, volume 4, Annex 13, Manufacture of Investigational Medicinal Products - Brussel. European Commission. Feb 2010.

39 Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009; 28(4):586-604.

40 Rohmeyer, K. and Klinglmueller, F. gMCP: Graph Based Multiple Test Procedures. R package version 0.8-8. 3 Oct 2014.

41 European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1). EMA . 2 Jul 2010.

42 National Academy of Sciences (NAS). The Prevention and Treatment of Missing Data in Clinical Trials. Washington D.C.: The National Academies Press, 2010.

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

44 Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. J Clin Invest 1987; 79(3):777-781.

45 Wenten M, Gaebler JA, Hussein M, Pelletier EM, Smith DB, Girase P et al. Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medication: a follow-up study. Diabet Med 2012; 29(11):1412-1418.

46 Yang L, He Z, Tang X, Liu J. Type 2 diabetes mellitus and the risk of acute pancreatitis: a meta-analysis. Eur J Gastroenterol Hepatol 2013; 25(2):225-231.

47 Standards of medical care in diabetes. Diabetes Care 2014; 37(Supplement 1):S14-S80.

48 International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. Dec 2014.

49 Novo Nordisk: http://novonordisk-trials.com/website/content/how-we-disclose-trial-information.aspx.

Protocol

Protocol final version 1.0, dated 14 July 2015, including:

Protocol amendment no. 01-PT, dated 18 February 2016

Protocol amendment no. 02-Global, dated 28 October 2016

Trial ID: NN9535-4216

Efficacy and safety of semaglutide versus dulaglutide as add-on to metformin in subjects with type 2 diabetes

Trial phase: 3b

Protocol originator

[redacted], [redacted]

Trial Operations, Semaglutide Diabetes & Diabetes Outcomes

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List of abbreviations

ADA	American Diabetes Association
AACE	American Association of Clinical Endocrinologists
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under curve
BG	blood glucose
BMI	body mass index
CABG	coronary artery bypass graft surgery
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLAE	clinical laboratory adverse event
C_{max}	maximum concentration
CRF	case report form
CT	computerised axial tomography
DFU	direction for use
DPP-4	ubiquitous dipeptidyl peptidase
DTSQ	Diabetes Treatment Satisfaction Questionnaire
DUN	dispensing unit number
EAC	event adjudication committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EMA	European Medicines Agency
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit
FPG	fasting plasma glucose
GCP	Good Clinical Practice

GLP-1	glucagon-like peptide-1
HbA_{1c}	glycosylated haemoglobin
HDL	high density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgE	immunoglobulin E
IND	Investigational New Drug Application
IRB	institutional review board
IWRS	interactive web response system
i.v.	intravenous
LC-MS/MS	liquid chromatography coupled with tandem mass spectrometry
LDL	low density lipoprotein
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LPFV	last patient first visit
LPLV	last patient last visit
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MESI	medical event of special interest
MI	myocardial infarction
MMRM	model for repeated measures
MRI	magnetic resonance imaging
NA or N/A	not applicable
ND	not done
NOAEL	no observable adverse effect level
NYHA	New York Heart Association
OAD	oral antidiabetic drug
P	phone contact
PCI	percutaneous coronary intervention
PG	plasma glucose

PP	per protocol
PRO	patient reported outcome
QALY	quality adjusted life years
RA	receptor agonist
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous(ly)
SF-36v2™	short form health survey
SMPG	self-measured plasma glucose
SmPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
T2D	type 2 diabetes
TEAE	treatment emergent adverse event
TIA	transient ischaemic attack
t_{max}	time to maximum concentration
TSH	thyroid-stimulating hormone
UNL	upper normal limit
UNR	upper normal range
UTN	Universal Trial Number
V	visit

1 Summary

Objective(s) and endpoint(s):

Primary objective

To compare the effect of once-weekly dosing of two dose levels of subcutaneous semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of two dose levels of subcutaneous dulaglutide (0.75 mg and 1.5 mg) on glycaemic control in subjects with type 2 diabetes on a background treatment with metformin.

Primary endpoint

Change from baseline to week 40 in HbA_{1c}

Key secondary objective

To compare the effect of once-weekly dosing of two dose levels of subcutaneous semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of two dose levels of subcutaneous dulaglutide (0.75 mg and 1.5 mg) in subjects with type 2 diabetes on a background treatment with metformin with regards to:

- Body weight control
- Blood pressure
- Patient reported outcomes
- Safety and tolerability

Key secondary endpoints

- Change from baseline to week 40 in body weight (kg)

Change from baseline to week 40 in:

- Fasting plasma glucose
- Systolic and diastolic blood pressure
- Overall scores for patient reported outcomes: Diabetes Treatment Satisfaction Questionnaire

Subjects who after 40 weeks treatment achieve (yes/no):

- HbA_{1c} ≤6.5% (48 mmol/mol) American Association of Clinical Endocrinologists target

Trial design:

The trial is a 40-week randomised, open-label, active-controlled, parallel group, multicentre, multinational, four-armed trial.

Subjects with type 2 diabetes inadequately controlled with metformin alone will after approximately 2 weeks screening period be randomised in a 1:1:1:1 manner to receive either a dose of 0.5 mg or 1.0 mg of semaglutide once-weekly or 0.75 mg or 1.5 mg of dulaglutide once-weekly.

After the treatment period of approximately 40 weeks in total, all subjects enter a follow-up period of 5 weeks ended by a follow-up phone contact. Total trial duration for the individual subjects will be approximately 47 weeks.

Trial population:

A planned total number of 1196 subjects will be randomised.

Key inclusion criteria

- Male or female, age ≥ 18 years at the time of signing informed consent.
- HbA_{1c} 7.0 – 10.5% (53 – 91 mmol/mol) (both inclusive)
- Subjects on stable diabetes treatment with metformin (minimum of 1500 mg/day or maximal tolerated dose documented in the patient medical record) for 90 days prior to screening

Key exclusion criteria

- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice).
- Any condition, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol
- Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening. An exception is short-term insulin treatment for acute illness for a total of ≤14 days
- History of pancreatitis (acute or chronic)
- Screening calcitonin ≥50 ng/L
- Family or personal history of Multiple Endocrine Neoplasia Type 2 or Medullary Thyroid Carcinoma
- Renal impairment defined as eGFR < 60 mL/min/1.73 m^2 as per CKD-EPI
- Subjects presently classified as being in New York Heart Association Class IV
- Planned coronary, carotid or peripheral artery revascularisation on the day of screening
- Proliferative retinopathy or maculopathy requiring acute treatment
- History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas)
- Anticipated initiation or change in concomitant medications (for more than 14 consecutive days or on a frequent basis) known to affect weight or glucose metabolism (e.g. orlistat, thyroid hormones, corticosteroids)

Assessments:

- Glucose metabolism (HbA_{1c}, fasting plasma glucose)
- Body measurements (weight (in kg), body mass index (BMI) and waist circumference)
- Blood pressure (sitting)
- Fasting blood lipids (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides)
- Self-measured plasma glucose (7-point profile)
- Patient reported outcomes
- Adverse events and serious adverse events
- Hypoglycaemic episodes
- Biochemistry and haematology
- Pulse
- Calcitonin
- Physical examination
- Electrocardiogram

Trial product(s):

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

- Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Dulaglutide, solution for injection, 0.75 mg/0.5 mL in a pre-filled pen
- Dulaglutide, solution for injection, 1.5 mg/0.5 mL in a pre-filled pen

2 Flow chart

Trial Periods	Screening	Randomisation	Treatment						End of treatment[1] (EOT)	Follow-up[1]	EOT Premature discontinuation[2]	Follow-up Premature discontinuation[2]
Visit (V)/ phone contact (P)	V1	V2	V3	P4	V5	V6	V7	V8	V9	P10	V9A	P10A
Timing of visit (weeks)	-2	0	4	6	8	12	16	28	40	45		
Visit window (days)	±7		±3	±3	±3	±3	±3	±3	±7	+7		
SUBJECT RELATED INFO/ASSESSMENTS												
Informed consent	X											
In/exclusion criteria	X	X										
Randomisation		X										
Concomitant illness	X											
Medical history	X											
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Demography	X											
Diagnosis of diabetes	X											
Tobacco use	X											
History of cardiovascular disease	X											
History of gallbladder disease	X											
Withdrawal criteria			X	X	X	X	X	X	X		X	
EFFICACY												
Height		X										
Body weight		X	X		X	X	X	X	X		X	
BMI		X	X		X	X	X	X	X		X	
Waist circumference		X					X		X		X	
Blood pressure, sitting	X	X	X		X	X	X	X	X		X	
Fasting plasma glucose		X	X		X	X	X	X	X		X	
HbA_{1c}	X	X	X		X	X	X	X	X		X	
Lipids		X					X		X		X	
7-point profile		X					X		X		X	

Trial Periods	Screening	Randomisation	Treatment						End of treatment[1] (EOT)	Follow-up[1]	EOT Premature discontinuation[2]	Follow-up Premature discontinuation[2]
Visit (V)/ phone contact (P)	V1	V2	V3	P4	V5	V6	V7	V8	V9	P10	V9A	P10A
Timing of visit (weeks)	-2	0	4	6	8	12	16	28	40	45		
Visit window (days)	±7		±3	±3	±3	±3	±3	±3	±7	+7		
PRO questionnaires		X					X		X		X	
SAFETY												
Adverse events		X[3]	X	X	X	X	X	X	X	X	X	X
Hypoglycaemic episodes	X	X	X	X	X	X	X	X	X	X	X	X
ECG[4]		X					X		X		X	
Fundoscopy/Fundus photography[5]		X										
Physical examination	X						X		X		X	
Pulse, sitting	X	X	X		X	X	X	X	X		X	
Biochemistry		X	X		X		X	X	X		X	
Creatinine (including eGFR)	X	X	X		X		X	X	X		X	
Haematology		X	X		X		X	X	X		X	
Pregnancy test[6]	X	X							X		X	
Calcitonin	X						X		X		X	
TRIAL MATERIAL												
Dispensing visit		X			X		X	X				
Drug accountability					X		X	X	X		X	
IWRS call	X	X			X		X	X	X		X	
REMINDERS												
End of trial										X		
Attend visit fasting[7]		X	X		X	X	X	X	X		X	
Direction for use (DFU)		X										
Dispense diary	X	X	X		X	X	X	X	X		X	
Collect and review diary[8]		X	X		X	X	X	X	X		X	
Dispense blood glucose meter	X											
Hand out subject ID card	X											
Training in pen handling		X	X									

Footer	Description
x[1]	V9 (End of treatment) and P10 (Follow-up) are applicable for all randomised subjects, except for subjects who are withdrawn. Subjects who have discontinued trial product prematurely should also attend V9 and P10 according to their initially scheduled week 40 and week 45 visits.
x[2]	Subjects discontinuing trial product prematurely will be asked to attend two additional visits to undergo assessments: End of treatment - premature discontinuation (V9A) and Follow-up - premature discontinuation (P10A). V9A should be scheduled as soon as possible after discontinuation of the trial product. P10A should be scheduled 5 weeks after discontinuation of trial product (+7 days visit window). If a subject withdraws from the trial, the investigator must aim to undertake procedures similar to those for V9A as soon as possible after discontinuation of trial product and P10A should be scheduled 5 weeks after the subject has discontinued trial product (+7 days window). If a subject has already prematurely discontinued from trial product and previously attended visit 9A (end of treatment) and follow-up phone contact (10A), no further visits should be attended.
x[3]	Includes AEs from the first trial-related activity after the subject has signed the informed consent at V1. Procedures and assessments performed at visit 1 and/or 2 are considered screening procedures. The result of these procedures should be considered pre-existing conditions and should be reported as medical history or concomitant illness.
x[4]	ECG performed within 7 days prior to the screening visit is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime.
x[5]	Fundoscopy/fundus photography performed within 90 days before visit 2 is acceptable if results are available for evaluation at the visit 2 and no deterioration in visual function since last assessment.
x[6]	For women of child bearing potential: For site visits 1, 9 and 9A a serum pregnancy test must be performed. At the randomisation visit, a urine pregnancy test must be performed prior to randomisation. In case a menstrual period is missed or if pregnancy is suspected at any time during the trial, a urine pregnancy test should be performed. The subject should be instructed not to dose trial product before pregnancy has been ruled out.
x[7]	Fasting is defined as having consumed only water within the last 6 hours prior to visit. Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed but other prescribed medication should be taken as prescribed.
x[8]	If any hypoglycaemic events are reported at P10 or P10A, information related to hypoglycaemic event(s) should be documented in the subject's medical record and the entry in the medical record will be considered source data.

3 Background information and rationale for the trial

The trial will be conducted in compliance with this protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP)[1] and applicable regulatory requirements, and in accordance with the Declaration of Helsinki.[2]

In this document, the term investigator refers to the individual responsible for the overall conduct of the clinical trial at a trial site.

3.1 Background information

3.1.1 Type 2 diabetes

Type 2 diabetes (T2D) is a progressive metabolic disease primarily characterised by abnormal glucose metabolism. The pathogenesis is not fully understood but seems to be heterogeneous, involving environmental, lifestyle, and genetic factors leading to chronic hyperglycaemia caused by peripheral tissue insulin resistance, impaired insulin secretion due to abnormal beta-cell function and abnormal glucose metabolism in the liver.[3]

Optimal glycaemic control is the treatment goal in subjects with T2D in order to prevent long-term complications associated with chronic hyperglycaemia.[4] Despite the availability of several antidiabetic drugs and insulin, a significant proportion of subjects with T2D do not achieve the recommended blood glucose (BG) target levels.[5, 6]

3.1.2 Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the L-cells in the small intestine. An incretin hormone is a gut-derived peptide with important physiological function in augmenting postprandial insulin secretion in response to ingestion of a meal. GLP-1 has a glucose-dependent stimulatory effect on insulin and inhibitory effect on glucagon secretion from the pancreatic islets (i.e. when plasma glucose (PG) levels are above normal).[7, 8] Both these effects are considered of importance for the glucose lowering effect of GLP-1.[9] Physiologically, GLP-1 has a pronounced inhibitory effect on gastric emptying.[10] This effect seems to diminish upon chronic exposure to GLP-1.[11, 12] At supra-physiological levels GLP-1 also lowers body weight due to a decreased energy intake induced by a lowered appetite.[13]

Subjects with diabetes have a decreased incretin effect.[14-17] However, the insulinotropic action of GLP-1 and thus, the ability to lower BG is preserved in subjects with T2D when administered at supra-physiological levels.[18]

The mechanism of action makes GLP-1 a potent BG lowering agent[19] and thus an attractive pharmacological tool for treatment of T2D.[10, 20, 21] However, the very short elimination half-life ($t_{½}$) of endogenous GLP-1, $t_{½}$ <1.5 minutes after intravenous (i.v.) administration, due to rapid

degradation by ubiquitous dipeptidyl peptidase (DPP-4)[22] makes native GLP-1 an unattractive treatment option. Clinical trials have revealed that 24-hour infusion of native GLP-1 would be necessary to achieve satisfactory glycaemic control.[23] Therefore, to benefit from the potentials of GLP-1 in treatment of diabetes it has been necessary to develop GLP-1 receptor agonists (RA) with longer half-lives.

3.1.3 Semaglutide

Semaglutide is a potent human GLP-1 analogue for subcutaneous (s.c.) administration. It is structurally similar to liraglutide (Victoza®), a once-daily GLP-1 analogue developed by Novo Nordisk and approved worldwide for the treatment of T2D.

For the semaglutide molecule the principal mechanism of protraction is albumin binding facilitated by a large fatty acid derived chemical moiety attached to the lysine in position 26. The specific modifications in the molecule are: 1) a modification in position 8 (alanine to 2-aminoisobutyric acid) of the peptide backbone in order to further increase stability against DPP-4, and a change in position 34 from a lysine to an arginine in order to only have one (1) lysine in the sequence; 2) a large hydrophilic linker between the lysine in position 26 and the gamma glutamate whereto the fatty acid is attached; 3) a C18 fatty di-acid with a terminal acidic group. The latter two (2) contribute to increased albumin binding which results in decreased renal clearance. In addition to slowed degradation in plasma and decreased renal clearance, delayed absorption from subcutis possibly also contributes to a prolonged half-life $t_{½}$ of 155-183 hours.

In vitro receptor studies have shown that semaglutide is a potent and selective GLP-1 analogue, and animal studies using non-diabetic rats, non-diabetic pigs and diabetic mice have shown lowering of BG and inhibition of food intake. A clinically relevant effect on glucose metabolism and body weight has also been observed in humans.

3.1.4 Nonclinical data - semaglutide

The nonclinical programme for semaglutide was designed according to the ICH M3[24] guideline to support the clinical development. The standard nonclinical data package required to support phase 3 clinical trials has been completed. In addition, 2-year carcinogenicity studies and a pre- and postnatal development toxicity study have been completed.

Semaglutide is generally well tolerated with expected GLP-1 effects on food intake and body weight being dose limiting in mice, rats and cynomolgus monkeys. Two potential safety issues have been identified.

3.1.4.1 Thyroid C-cell tumours in rodents

Treatment-related non-genotoxic proliferative changes in the thyroid C-cells of mice and rats were observed in 2-year carcinogenicity studies with semaglutide. Early C-cell changes were also

identified in repeated dose toxicity studies with semaglutide in mice. However, this was not the case in other species including a 52-week repeat dose study in non-human primates at exposure levels up to 36-fold above the expected clinical exposure. The observed pattern of effects in mice and rats (thyroid C-cell proliferation preceded by increase in serum calcitonin) and lack of these effects in the non-human primate and in man suggest that the mechanism by which semaglutide acts on the thyroid C-cells in rodents is the same as has been demonstrated for other GLP-1 RAs, including liraglutide. The relevance for human subjects is unknown. Recently published data have shown that the GLP-1 receptor is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor mediated C-cell changes in humans is considered to be low.[25]

3.1.4.2 Teratogenicity in rats

Semaglutide has been concluded teratogenic in rats, with exposure at no observable adverse effect level (NOAEL) below expected human exposure. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function which is specific to rats.

Non-human primates and humans do not depend on a yolk sac with placental function to supply nutrients to the embryo early in pregnancy. The effect on rat embryo-foetal development is therefore not likely to be relevant to humans as described below. Preliminary and main embryo-foetal development and pre- and postnatal development studies with doses corresponding to 12-15 fold expected clinical exposure in cynomolgus monkeys have been finalised. In the main embryo-foetal development study sporadic abnormalities were reported across all dose groups and in the pre- and postnatal development study a dose-dependent increase in early pregnancy losses was observed. The findings observed across the three studies in cynomolgus monkeys are not indicative of a teratogenic potential of semaglutide in this species. The increase in early pregnancy losses is indicative of embryo-toxicity, which may be related to the maternal effect of semaglutide (marked body weight loss). A developmental toxicity NOAEL was determined at an exposure 1- to 2 fold the expected clinical exposure (1 mg/week). A risk for the developing human embryo or foetus cannot be definitely ruled out, but the absence of findings indicative of teratogenicity in the embryo-foetal development and pre- and postnatal development studies in cynomolgus monkey decreases the level of concern.

A comprehensive review of results from the nonclinical studies can be found in the current edition of semaglutide (NN9535) Investigator's Brochure (IB),[26] or any updates hereof.

3.1.5 Clinical data - semaglutide

As of 20 December 2014, six clinical pharmacology trials (trials 1820, 3679, 3633, 3616, 3819 and 4010) and one phase 2 trial (trial 1821) have been completed with semaglutide s.c. In the completed trials, 553 subjects have been exposed to semaglutide: 192 healthy subjects (both single and multiple dosing), 313 subjects with T2D (up to 12 weeks treatment) and 48 subjects with varying

degrees of renal impairment (four with T2D) (single dosing). In addition, 22 healthy subjects have been exposed to semaglutide s.c. in the oral administration semaglutide project (trials NN9924-3691 and NN9924-3692).

As of 20 December 2014, 8 therapeutic confirmatory trials are ongoing with semaglutide s.c. The efficacy and safety of semaglutide s.c. dosing once weekly is compared versus placebo in drug naïve subjects (trial 3623), versus the DPP-4 inhibitor sitagliptin (trial 3626), versus exenatide extended release (trial 3624), versus basal insulin (trial 3625) and versus placebo as add on to basal insulin (trial 3627). In addition, a long-term (104 weeks) trial is ongoing to compare the long-term safety (including cardiovascular risk) and efficacy versus placebo as add-on to standard-of-care treatment (trial 3744). Finally, two trials are being conducted in Japanese subjects with T2D in which the efficacy and safety of semaglutide as monotherapy is compared to sitagliptin monotherapy (trial 4092) and semaglutide (0.5 mg and 1.0 mg) in monotherapy or in combination with one oral antidiabetic drug (OAD) (either of sulfonylurea, glinide, α-glucosidase inhibitor or thiazolidinedione) is compared with OAD therapy in subjects who are insufficiently controlled on diet/exercise therapy or OAD monotherapy (either of sulfonylurea, glinide, α-glucosidase inhibitor or thiazolidinedione) (trial 4091). In parallel, 10 clinical pharmacology trials are ongoing (trials 3817, 3789, 3652, 3685, 3634, 3684, 3651, 3635, 3687 and 3818) to investigate the metabolism of semaglutide, the impact of hepatic impairment on the pharmacokinetic profile of semaglutide and the effect of semaglutide on several aspects of glycaemic control, appetite regulation, QTc-prolongation and drug-drug interaction with selected oral drugs. These investigations are being performed in different populations including healthy subjects, subjects with T2D, obese subjects and subjects with hepatic impairment.

3.1.5.1 Pharmacokinetics

Results from two single dose trials (NN9535-3616 and NN9535-4010) and from one multidose trial (NN9535-3819) based on the LC-MS/MS assay demonstrated a median time to maximum concentration (t_{max}) of 24-96 hours post dosing and a $t_{½}$ in the range of 155-183 hours. Overall, the pharmacokinetic properties of semaglutide appear similar in Caucasian and Japanese subjects and also in healthy subjects and subjects with T2D. In a trial with subjects with different degrees of renal impairment (NN9535-3616), data suggested that subjects with severe renal impairment had a slightly higher exposure compared to subjects with normal renal function. Area under curve ($AUC_{0-\infty}$) increased by approximately 22% in subjects with severe renal impairment whereas subjects with mild or moderate renal impairment and subjects on haemodialysis had exposure similar to subjects with normal renal function. No safety signals were identified in either of the renal groups and tolerability profiles appeared similar across renal groups; thus a dose-reduction in subjects with severe renal impairment does not appear to be warranted.

Interaction with oral contraceptives was assessed at semaglutide 1.0 mg steady-state exposures in postmenopausal women with T2D (NN9535-3819). Steady-state exposures (AUC_{0-24h}) of

ethinylestradiol and levonorgestrel were slightly increased, with bioequivalence criterion met for ethinylestradiol but not for levonorgestrel; the increase was seen when oral contraceptives were coadministered with semaglutide compared to oral contraceptives alone. The bioequivalence criterion was met for maximum concentration (C_{max}) of both ethinylestradiol and levonorgestrel. These data indicate that semaglutide does not decrease the exposure of oral contraceptives, and suggest that no adjustments of oral contraceptive dose are warranted for women of childbearing potential using a low-dose oral contraceptive.

3.1.5.2 Efficacy

As of 20 December 2014, efficacy of semaglutide in the target population - subjects with T2D has been investigated in one phase 2 dose range finding trial (NN9535-1821). The trial was a 12-week, randomised, double-blind, placebo- and active-controlled trial in which 411 adults with T2D received once-weekly s.c. injection of 1 of 5 semaglutide dose levels (0.1-1.6 mg), once-daily injection of open label liraglutide (1.2 mg or 1.8 mg) or once-weekly placebo.

12 weeks of treatment, equivalent to 5-7 weeks in steady state on maintenance dose, provided statistically significant and clinically relevant improvement in glycaemic control for dose levels of 0.2 mg and above. Mean changes in glycosylated haemoglobin (HbA_{1c}) from baseline was up to -1.19% (placebo adjusted estimated treatment difference). Dose-dependent improvements in fasting plasma glucose (FPG) and postprandial PG were also observed. The improvement in glycaemic control was accompanied by weight loss for semaglutide doses of 0.8 mg and above (estimated treatment difference compared to placebo up to a mean value of -3.64 kg).

3.1.5.3 Safety

From the clinical trials completed so far the following safety observations have been made. In consistency with the findings obtained from evaluating other GLP-1 RAs, common adverse events (AEs) included nausea and vomiting; most of them were mild to moderate in severity. Hypoglycaemia has occurred in subjects receiving semaglutide and these events have mainly been minor. As with other GLP-1 RAs, an increase in heart rate has been observed in subjects exposed to semaglutide . The implications of this increase are unknown. As with all protein based pharmaceuticals, subjects treated with semaglutide may develop immunogenic and allergic reactions. Few allergic reactions have been reported in connection with semaglutide. These have mainly been mild and transient however, more generalised reactions may occur, including urticaria, rash, pruritus and rare cases of angioedema have been observed. Injection site reactions have been infrequently reported. These have mainly been mild and transient in nature.

Please see the current edition of semaglutide (NN9535) IB[26] or any updates hereof for further details.

For an assessment of benefits and risks of the trial, see section 18.1.

3.1.6 Dulaglutide

Dulaglutide is a GLP-1 RA with prolonged action developed and marketed by Eli Lilly and Company, IN, US under the trade name Trulicity®. Dulaglutide has recently been approved in the US and in the EU for use as once-weekly s.c. injection for treatment of T2D. Dulaglutide has shown non-inferiority on glycaemic control versus liraglutide, but significantly less weight loss.[27]

Dulaglutide belongs to the same class of drugs as semaglutide and as such they share many of the same efficacy and safety characteristics. As dulaglutide is a marketed drug its characteristics are described in the EU summary of product characteristics (SmPC),[28] US prescribing information[29] and the local prescribing information (non-US and non-EU countries) for dulaglutide (Trulicity®).

3.2 Rationale for the trial

The currently available treatment modalities for T2D are still not satisfactory and there is a large proportion of subjects not reaching the treatment targets despite a high level of compliance with the treatment regimens. Furthermore, there is a segment of subjects where either compliance with once-daily treatment regimens is an issue resulting in sub-optimal glycaemic control, or where there is a wish for a more convenient treatment regimen.

The aim for the present trial is to compare semaglutide once-weekly versus dulaglutide once-weekly as addition to metformin in a population of subjects with T2D in terms of glycaemic control, weight control and other efficacy parameters. Furthermore, the trial is designed to address and compare tolerability, patient well-being and treatment satisfaction.

4 Objective(s) and endpoint(s)

4.1 Objective(s)

Primary objective

To compare the effect of once-weekly dosing of two dose levels of s.c. semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of two dose levels of s.c. dulaglutide (0.75 mg and 1.5 mg) on glycaemic control in subjects with T2D on a background treatment with metformin.

Secondary objective

To compare the effect of once-weekly dosing of two dose levels of s.c. semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of two dose levels of s.c. dulaglutide (0.75 mg and 1.5 mg) in subjects with T2D on a background treatment with metformin with regards to:

- Body weight control
- Blood pressure and fasting blood lipids
- Patient reported outcomes
- Safety and tolerability

4.2 Endpoint(s)

4.2.1 Primary endpoint

- Change from baseline to week 40 in HbA_{1c}

4.2.2 Secondary endpoints

4.2.2.1 Confirmatory secondary endpoint

- Change from baseline to week 40 in body weight (kg)

4.2.2.2 Supportive secondary endpoints

Supportive secondary efficacy endpoints

Change from baseline to week 40 in:

- FPG*
- Self-measured plasma glucose (SMPG), 7-point profile
    - Mean 7 point profile
    - Mean post prandial increment (over all meals)
- Fasting blood lipids (total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides)
- BMI and waist circumference

- Systolic and diastolic blood pressure*
- Overall scores for patient reported outcomes
    - Short Form health survey (SF-36v2™)
    - Diabetes Treatment Satisfaction Questionnaire (DTSQ)*

Subjects who after 40 weeks treatment achieve (yes/no):

- HbA_{1c} <7.0% (53 mmol/mol) American Diabetes Association (ADA) target
- HbA_{1c} ≤6.5% (48 mmol/mol) American Association of Clinical Endocrinologists (AACE) target*
- Weight loss ≥5%
- Weight loss ≥10%
- HbA_{1c} <7.0% (53 mmol/mol) without severe or BG confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA_{1c} reduction ≥1%
- Weight loss ≥3%
- HbA_{1c} reduction ≥1% and weight loss ≥3%

Supportive secondary safety endpoints

- Number of treatment emergent adverse events (TEAEs)
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemia episodes
- Treatment emergent severe or BG confirmed symptomatic hypoglycaemia episodes (yes/no)

Change from baseline to week 40 in:

- Haematology
- Biochemistry
- Calcitonin
- Pulse
- Electrocardiogram (ECG) category
- Physical examination

* Key supportive secondary endpoint prospectively selected for disclosure (e.g. clinicaltrials.gov and EudraCT)

5 Trial design

5.1 Type of trial

The trial is a 40-week randomised, open-label, active-controlled, parallel group, multicentre, multinational, four-armed trial.

Subjects with T2D inadequately controlled with metformin alone will after approximately 2 weeks screening period be randomised in a 1:1:1:1 manner to receive either a dose of 0.5 mg or 1.0 mg of semaglutide once-weekly or 0.75 mg or 1.5 mg of dulaglutide once-weekly.

After the treatment period of approximately 40 weeks in total, all subjects enter a follow-up period of 5 weeks ended by a follow-up phone contact. Total trial duration for the individual subjects will be approximately 47 weeks. The trial design is summarised schematically in Figure 5–1.

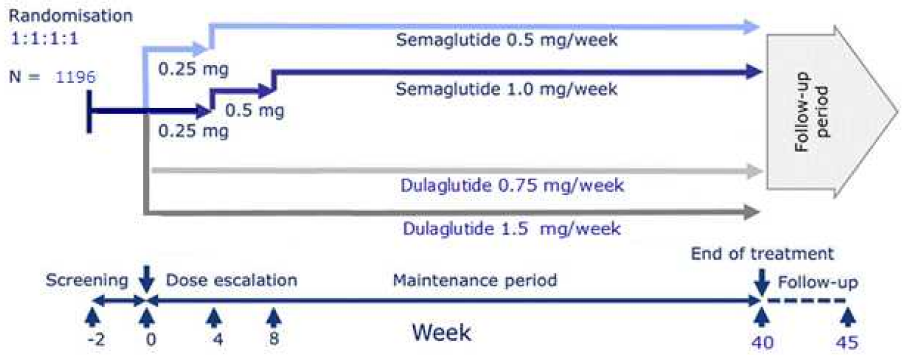


Figure 5–1 Trial design

5.2 Rationale for trial design

The aim for the trial is to compare the efficacy of semaglutide 0.5 mg once-weekly versus dulaglutide 0.75 mg once-weekly and the efficacy of semaglutide 1.0 mg once-weekly versus dulaglutide 1.5 mg once-weekly in subjects with T2D in terms of glycaemic control, weight control and other efficacy parameters. Furthermore, the trial is designed to address and compare tolerability, patient well-being and treatment satisfaction. The in- and exclusion criteria allow for enrolment of a broad trial population and include subjects with mild renal impairment. The treatment duration of 40 weeks is considered adequate for assessment of efficacy, safety, tolerability and patient satisfaction.

5.3 Treatment of subjects

Semaglutide treatment

Subjects randomised to semaglutide will follow a fixed dose escalation. The maintenance dose of 0.5 mg will be reached after 4 doses (4 weeks) of 0.25 mg. The maintenance dose of 1.0 mg will be reached after 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg. After the maintenance dose is reached, the dose must not be changed during the course of the trial unless due to safety reasons.

Dulaglutide treatment

Subjects randomised to dulaglutide will receive a dose of either 0.75 mg or 1.5 mg dulaglutide once-weekly without dose escalation. The randomisation dose must not be changed during the course of the trial unless due to safety reasons.

Table 5–1 Treatment of subjects

Trial periods		**Screening**	**Treatment**	**Treatment**	**Treatment**	**Follow-up**
Duration of each period		2 weeks	4 weeks	4 weeks	32 weeks	5 weeks
Treatment arm	**N**					
Semaglutide 0.5 mg	299	Screening	Semaglutide 0.25 mg	Semaglutide 0.5 mg	Semaglutide 0.5 mg	Follow-up
Semaglutide 1.0 mg	299	Screening	Semaglutide 0.25 mg	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Follow-up
Dulaglutide 0.75 mg	299	Screening	Dulaglutide 0.75 mg	Dulaglutide 0.75 mg	Dulaglutide 0.75 mg	Follow-up
Dulaglutide 1.5 mg	299	Screening	Dulaglutide 1.5 mg	Dulaglutide 1.5 mg	Dulaglutide 1.5 mg	Follow-up

5.3.1 Background medication

The only allowed diabetes background medication is metformin. Subjects must upon inclusion continue pre-trial dose of background medication throughout the entire trial unless the subject meets the rescue criteria, see section 6.4.

Metformin

Metformin is considered background medication and will not be provided by Novo Nordisk A/S. Metformin should be used in accordance with standard of care in the individual country at the discretion of the investigator. However, the maximum approved dose in the individual country must not be exceeded.

Only applicable for Slovakia: All antidiabetic medication will be reimbursed by Novo Nordisk Slovakia s.r.o.

5.3.2 Injection site

Injections should be administered in the thigh, abdomen or upper arm, at any time of the day irrespective of meals. Injections should be administered on the same day of the week during the trial. Injections should not be administered intravenously or intramuscular.

5.3.3 Missed dose

If a semaglutide dose is missed, it should be administered as soon as noticed, provided the time to the next scheduled dose is at least 2 days (48 hours). If a dose is missed and the next scheduled dose is less than 2 days (48 hours) away, the subject should not administer a dose until the next scheduled dose. A missed dose should not affect the scheduled dosing day of the week.

If a dulaglutide dose is missed, it should be administered as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose. If less than 3 days (72 hours) remain before the next scheduled dose, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, subject can then resume their regular once weekly dosing schedule.

5.4 Treatment after discontinuation of trial product

When discontinuing trial products the subject should be switched to a suitable marketed product at the discretion of the investigator.

5.5 Rationale for treatment

Semaglutide has been developed for s.c. administration. The doses of 0.5 mg and 1.0 mg once-weekly have been chosen based on careful evaluation to strike a satisfactory balance of efficacy and safety that would satisfy the majority of subjects. Hence, the duration and the dose of the randomised treatments are considered adequate for obtaining meaningful information on efficacy and safety in accordance with the trial objectives. Subjects will enrol for a treatment period of 40 weeks in order to be able to evaluate full effect and durability of the primary and secondary endpoints as well as reasonable safety assessment.

6 Trial population

6.1 Number of subjects

Number of subjects planned to be screened:	1994
Number of subjects planned to be randomised:	1196
Number of subjects expected to complete the trial*:	897

*Number of subjects expected to complete the trial on randomised trial product without rescue medication.

6.2 Inclusion criteria

For an eligible subject, all inclusion criteria must be answered “yes”.

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
2. Male or female, age ≥ 18 years at the time of signing informed consent
3. Subjects with T2D diagnosed clinically ≥ 90 days prior to screening
4. HbA_{1c} 7.0 – 10.5% (53 – 91 mmol/mol) (both inclusive)
5. Subjects on stable diabetes treatment with metformin (minimum of 1500 mg/day or maximal tolerated dose documented in the patient medical record) for 90 days prior to screening

6.3 Exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no".

1. Known or suspected hypersensitivity to trial product(s) or related products
2. Previous participation in this trial. Participation is defined as signed informed consent
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice). *Germany: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or sexual abstinence or vasectomised partner. Ireland: Adequate contraceptive measures are defined as established use of combined oral contraceptives, injected or implanted hormonal methods of contraception, sterilisation, intrauterine device or intrauterine system or consistent use of barrier methods together with the use of spermicide and sexual abstinence. United Kingdom: Adequate contraceptive measures are defined as established use of oral, intravaginal, transdermal combined estrogen and progestogen hormonal methods of contraception; oral, injected or implanted progestogen only hormonal*

methods of contraception; placement of an intrauterine device or intrauterine hormone releasing system, bilateral tubal occlusion, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), female sterilisation, vasectomised partner (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle). Portugal: Only highly effective methods of birth control (i.e. one that results in less than 1% per year failure rate when used consistently) are accepted, such as sexual abstinence (when in line with the preferred and usual lifestyle), combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion or vasectomised partner.

4. Receipt of any investigational medicinal product within 90 days before screening
5. Any condition, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol
6. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening. An exception is short-term insulin treatment for acute illness for a total of ≤14 days
7. History of pancreatitis (acute or chronic)
8. Screening calcitonin ≥50 ng/L
9. Family or personal history of Multiple Endocrine Neoplasia Type 2 or Medullary Thyroid Carcinoma
10. Renal impairment defined as eGFR < 60 mL/min/1.73 m^2 as per CKD-EPI
11. Any of the following: myocardial infarction (MI), stroke or hospitalisation for unstable angina and/or transient ischaemic attack (TIA) within the past 180 days prior to the day of screening
12. Subjects presently classified as being in New York Heart Association (NYHA) Class IV
13. Planned coronary, carotid or peripheral artery revascularisation on the day of screening
14. Proliferative retinopathy or maculopathy requiring acute treatment
15. History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas)
16. Anticipated initiation or change in concomitant medications (for more than 14 consecutive days or on a frequent basis) known to affect weight or glucose metabolism (e.g. orlistat, thyroid hormones, corticosteroids)

6.4 Rescue criteria

Subjects with persistent and unacceptable hyperglycaemia should be offered treatment intensification. If any of the FPG values exceed the limits outlined below and no intercurrent cause of the hyperglycaemia can be identified, a confirmatory FPG should be obtained by the central laboratory by calling the subject for a re-test as soon as possible:

- 15.0 mmol/L (270 mg/dl) from week 2 to end of week 7
- 13.3 mmol/L (240 mg/dl) from week 8 to end of week 13
- 11.1 mmol/L (200 mg/dl) from week 14 to end of treatment

If the confirmatory FPG also exceeds the values described above, the subject should be offered rescue medication in accordance with ADA/European Association for the Study of Diabetes[30] (excluding GLP RAs, DPP-4 inhibitors and amylin analogues). It is important for trial integrity that only subjects actually needing treatment intensification (as defined above) are started on rescue medication. Rescue medication (intensification of existing background medication and/or initiation of new antidiabetes medication) and any changes hereto should be captured on the concomitant medication form in the electronic case report form (eCRF), see section 8.2.4. Rescue medication should be prescribed as add-on to randomised treatment and subjects should continue to follow the protocol-specified visit schedule.

6.5 Premature discontinuation of trial product criteria

If any of the below trial product discontinuation criteria apply, the subject must be discontinued from trial product. The procedures in section 8.1.6 should be performed and the subject will not be withdrawn from the trial.

The subject must discontinue from trial product if the following applies:

- In case of pregnancy or intention to become pregnant
- A subject included in the trial in violation of the inclusion and/or exclusion criteria
- Simultaneous participation in any other clinical trial receiving an investigational medicinal product
- Due to a safety concern at the discretion of the investigator
- Calcitonin value ≥50 ng/L

The primary reason for discontinuation of trial product must be specified in the eCRF.

6.6 Withdrawal reason

The subject may withdraw at will at any time. The subject's request to discontinue must always be respected.

- Withdrawal of informed consent

Please see section 8.1.7 for procedures to be performed in case of subject withdrawal.

6.7 Subject replacement

Subjects who are withdrawn, initiated rescue medication or prematurely discontinue will not be replaced

6.8 Rationale for trial population

Subjects with T2D who are inadequately controlled on metformin will be included in the trial. Only serious concomitant conditions which could interfere with trial schedule and procedures preclude subjects from participating. The in- and exclusion criteria allow for enrolment of a broad trial population and include subjects with mild renal impairment.

7 Milestones

Planned duration of recruitment period (FPFV– LPFV): 24 weeks

Planned date for FPFV: 06-Jan-2016

Planned date for LPLV: 24-May-2017

End of trial is defined as LPLV.

Recruitment:
The screening and randomisation rate will be followed closely via the interactive web response system (IWRS) in order to estimate when to stop screening. All investigators will be notified immediately when the recruitment period ends, after which no further subjects may be screened and the IWRS will be closed for further screening. All subjects included in the screening period and eligible for randomisation can be randomised.

Trial registration:
Information of the trial will be disclosed at clinicaltrials.gov and novonordisk-trials.com. According to the Novo Nordisk Code of Conduct for Clinical Trial Disclosure,[31] it will also be disclosed according to other applicable requirements such as those of the International Committee of Medical Journal Editors,[32] the Food and Drug Administration Amendment Act,[33] European Commission Requirements[34, 35] and other relevant recommendations or regulations. If a subject requests to be included in the trial via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the subject. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

8 Methods and assessments

8.1 Visit procedures

The following sections describe the assessments and procedures. These are also included in the flow chart (see section 2) as well as visit numbers, timing of site and phone visits and visit windows during the trial period.

Informed consent must be obtained before any trial related activity, see section 18.2.

A completion session must be performed in the IWRS after completion of V9.

8.1.1 Investigator site log

The investigator must keep a subject screening log, a subject identification code list and a subject enrolment log. The subject screening log and subject enrolment log may be combined in one list and may be generated from IWRS.

In addition, the investigator must keep a log of staff and a delegation of task(s) list at the trial site. Investigator must sign the log of staff and the delegation of task(s) at the trial site prior to the delegation of tasks.

8.1.2 Screening, visit 1

At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff. Subjects should be instructed to return the card to the investigator at the last trial visit or to destroy the card after the last visit.

Each subject will be assigned a unique 6-digit subject number which will remain the same throughout the trial.

8.1.3 Screening failures

For screening failures the screening failure form in the case report form (CRF) must be completed with the reason for not continuing in the trial. Serious adverse events (SAEs) from screening failures must be transcribed by the investigator into the eCRF. Follow-up of SAEs must be carried out according to section 12.

A screening failure session must be made in the IWRS and the screening failure form completed in the eCRF. The case book must be signed.

8.1.4 Re-screening

Re-screening is NOT allowed.

8.1.5 Fasting visits

The subjects should attend site visits in a fasting state (see section 2 for details). Fasting is defined as having consumed only water within the last 6 hours prior to the visit. If the subject does not attend the visit in a fasting state, the subject should be asked to attend a re-scheduled visit within the visit window to have the fasting assessments performed.

Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed but other prescribed medication should be taken according to prescription.

8.1.6 Premature discontinuation of trial product

If a subject is prematurely discontinued from trial product, the investigator must aim to undertake procedures similar to those for visit 9A (end of treatment) as soon as possible and the follow-up phone contact (phone contact 10A) should be performed five weeks after premature treatment discontinuation (+ 7 days).

Subjects discontinuing trial product prematurely should continue with the scheduled site contacts after visit 9A and phone contact 10A have been conducted. If necessary, in order to retain the subject in the trial, site visits can be replaced by phone contacts after discontinuation of trial product. Furthermore, subjects prematurely discontinued from trial product must be asked to attend the planned visit (visit 9) taking place 40 weeks (± 7 days) after their randomisation date and the planned phone contact (phone contact 10) five weeks later (+ 7 days).

If the subject is not willing to attend one or more of the above mentioned visits, it should be documented in the subject's medical record that the subject has refused to attend the visit.

For subjects prematurely discontinued from trial product, final drug accountability must be performed and a treatment discontinuation session must be made in the IWRS. The reason for premature discontinuation of trial product must be recorded in subject's medical records and the eCRF.

8.1.7 Withdrawals

If a subject considers to withdraw from the trial, the investigator must aim to undertake procedures similar to those for visit 9A (end of treatment) as soon as possible and the follow-up phone contact (phone contact 10A) should be performed five weeks after premature treatment discontinuation (+ 7 days). If a subject has already prematurely discontinued from trial product and previously attended visit 9A (end of treatment) and follow-up phone contact (10A), no further visits should be attended.

For withdrawn subjects, the end-of-trial form including the primary reason for premature discontinuation of trial product must be completed, and final drug accountability must be performed even if the subject is not able to come to the trial site. A treatment discontinuation session must be

made in the IWRS, however if a subject has already prematurely discontinued from trial product and a treatment discontinuation session in IWRS has been done, no IWRS session should be completed. The case book must be signed.

Although a subject is not obliged to give his/her reason(s) for withdrawing from a trial, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

8.1.8 Investigator assessment

Review of diaries, PROs, laboratory reports, ECGs, fundoscopy/fundus photography, physical examination etc. must be documented with the investigator's or delegate's dated signature either on the front page of the documents and/or in the subject's medical record. The signed documents must be retained at the trial site as source documentation.

For ECGs, physical examinations and fundoscopy/fundus photography the evaluations must follow the categories:

- Normal
- Abnormal
  - Was the result clinically significant? (No/Yes)

The evaluation should be based on investigator's or delegate's judgment.

For laboratory report values outside the reference range, the investigator must specify whether the value is clinically significant or clinically non-significant. All laboratory printouts must be signed and dated by the investigator on the day of evaluation. The signed laboratory report is retained at the trial site as source documentation.

In case of abnormal clinical significant findings found as a result of screening procedures conducted at visit 1 or assessments revealing baseline conditions at visit 2, the investigator must state a comment in the subject's medical record and record this in the concomitant illness form in the eCRF. At subsequent visits, any clinically significant changes or new clinically significant findings must be reported as an AE according to section 12.

Investigator or trial site staff must review the diary to ensure that AEs, including overall change in health and concomitant medication, are reported.

If clarification of entries or discrepancies in the diary or PRO is needed, the subject must be questioned and a conclusion made in the subject's medical record. Care must be taken not to bias the subject.

8.2 Subject related information

8.2.1 Demography

Demography will be recorded at screening visit and consists of:

- Date of birth (according to local regulation)
- Sex
- Race (according to local regulation)
- Ethnicity (according to local regulation)

8.2.2 Tobacco use

Details of tobacco use must be recorded at the screening visit. Smoking is defined as smoking at least one cigarette, cigar or pipe daily. The collected information should include whether or not the subject smokes or has smoked.

8.2.3 Concomitant illness and medical history

A **concomitant illness** is any illness that is present at the start of the trial as described in section 8.1.8.

Medical history is a medical event that the subject has experienced in the past. Only relevant medical history as judged by the investigator should be reported.

The information collected for concomitant illness and medical history should include diagnosis, onset and date of resolution or continuation, as applicable.

Any change to a concomitant illness should be recorded during the trial. A clinically significant worsening of a concomitant illness must be reported as an AE.

8.2.3.1 Diagnosis of diabetes

The date of diagnosis of T2D will be recorded at the screening visit.

8.2.3.2 History of cardiovascular disease

Information related to history of cardiovascular disease (i.e. heart failure including NYHA class, hypertension or ischaemic stroke) or other risk factors for cardiovascular disease will be recorded in the eCRF at screening visit.

8.2.3.3 History of gallbladder disease

Information related to history of gallbladder disease (i.e. gallstone disease, cholecystitis) will be recorded in the eCRF at screening visit.

8.2.4 Concomitant medication

A **concomitant medication** is any medication, other than the trial product, which is taken during the trial, including the screening and follow-up periods.

Details of any concomitant medication must be recorded at the first visit (screening visit). Changes in concomitant medication, including antidiabetic treatment prescribed at the end of the treatment and rescue treatment, must be recorded at each visit as they occur and the eCRF should be updated accordingly.

The information collected for each concomitant medication includes trade name or generic name, indication, start date (only start year is applicable if more than one year) and stop date or continuation and total daily dose (applicable only for antidiabetic medication).

If a change is due to an AE, then this must be reported according to section 12. If the change influences the subject's eligibility to continue in the trial, the monitor must be informed.

8.3 Assessments for efficacy

8.3.1 Height, body weight and BMI

Height is measured without shoes in cm or inches and recorded to nearest ½ cm or ¼ inch.

Body weight should be measured without shoes and only wearing light clothing to the nearest kg/lb.

BMI will be calculated in the eCRF every time the weight is measured using the equation:

BMI = body weight (kg)/(height (m) x height (m)) [kg/m^2 = lb/in^2 x 703]

8.3.2 Waist circumference

The waist circumference is defined as the minimal abdominal circumferences located midway between the lower rib margin and the iliac crest.

The measurement of waist circumference should be performed and recorded in the eCRF. The waist circumference will be measured using a non-stretchable measuring tape. It should be recorded to the nearest ½ cm or ¼ inch using the same measuring tape throughout the trial.

The waist circumference should be measured in a standing position with an empty bladder and wearing light clothing with accessible waist. The subject should be standing with arms down their side and feet together. The tape should touch the skin but not compress soft tissue. The subject should be asked to breathe normally and the measurement should be taken when the subject is breathing out gently.

8.3.3 Blood pressure

Systolic and diastolic blood pressure should be measured in a sitting position after the subject has been resting for at least 5 minutes and by using the standard clinical practice at the trial site.

8.3.4 Blood samples

Blood samples will be drawn according to flow chart and analysed at the central laboratory to determine levels of the following efficacy laboratory parameters:

Glucose metabolism:

- HbA_{1c} and FPG

Lipids (all fasting):

- Total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides

8.3.5 Self-measured plasma glucose

At the screening visit, subjects will be provided with a blood glucose meter including lancets, plasma-calibrated test strips and control solutions as well as instructions for use. The subjects will be instructed in how to use the device, the instruction will be repeated as necessary during the trial.

The blood glucose meters use test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood are automatically calibrated to plasma equivalent glucose values, which will be shown on the display.

Subjects should be instructed in how to record the results of the SMPGs in the diaries. The record of each SMPG should include date, time and value. All data from the diary must be transcribed into the eCRF during or following the contact. If obtained via phone and a discrepancy is later detected, the values in the eCRF should be corrected.

8.3.6 7-point self-measured plasma glucose profile

The subject will be asked to perform a 7-point SMPG profile, preferably within one week prior to site visit according to the flowchart, on days where the subject does not anticipate unusual strenuous exercise.

Time points, including date and time, for the 7-point profile: before breakfast, 90 min after start of breakfast, before lunch, 90 minutes after start of lunch, before dinner, 90 min after start of dinner and at bedtime

8.4 Assessments for safety

8.4.1 Physical examination

A physical examination must be performed and include the following:

General appearance, skin, thyroid gland, respiratory system, cardiovascular system, gastrointestinal system including mouth, central and peripheral nervous system, and lymph node palpation

8.4.2 Pulse

Pulse (beats per minute) should be recorded at site visits after resting for 5 minutes in a sitting position.

8.4.3 Electrocardiogram – 12 lead

A 12-lead ECG must be performed and interpreted locally by the investigator as described in section 8.1.8.

It is allowed to perform the screening visit ECG between the screening visit and the randomisation visit. The results must be available prior to randomisation. An ECG performed for any reason unrelated to this trial within 7 days prior to the screening visit is acceptable provided no clinical symptoms suggestive of cardiac disease have occurred in the meantime.

If the ECG was performed as a part of routine clinical practice on/before the date when the subject has signed the informed consent, it must be documented in the medical records that the reason for performing the procedure is not related to this trial.

8.4.4 Fundoscopy/fundus photography

Fundoscopy/fundus photography will be performed by the investigator or a local ophthalmologist according to local practice. Result of the fundoscopy/fundus photography will be interpreted by the investigator as described in section 8.1.8. Dilation is not a requirement.

If a fundoscopy/fundus photography has been performed within 90 days prior to randomisation, the procedure does not need to be repeated, unless worsening of visual function since the last examination has been noted.

If the fundoscopy/fundus photography was performed as a part of routine clinical practise on/before the date when the subject has signed the informed consent, it must be documented in the medical records that the reason for performing the procedure was not related to this trial.

8.4.5 Blood samples

Blood samples will be drawn and analysed at the central laboratory to determine levels of the following laboratory parameters:

Biochemistry:

- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, bilirubin (total), alkaline phosphatase, potassium, sodium, calcium (total), amylase, lipase, calcitonin and creatinine, including eGFR (per CKD-EPI)

Haematology:

- Haemoglobin, haematocrit, erythrocytes, thrombocytes and leucocytes

Pregnancy test (females of child bearing potential):

- Serum beta-human chorionic gonadotropin

8.4.6 Pregnancy test

Females of childbearing potential will have a serum pregnancy test (beta-human chorionic gonadotropin) performed. At the randomisation visit, a urine pregnancy test must be performed prior to randomisation.

In case a menstrual period is missed or if pregnancy is suspected at any time during the trial, a urine pregnancy test should be performed. The subject should be instructed not to dose trial product before pregnancy has been ruled out.

Pregnancy testing will not be required (unless required by local law) for women of non-childbearing potential, such as but not limited to women who have undergone a hysterectomy, bilateral oophorectomy, bilateral tubal ligation or are postmenopausal (e.g. women above the age of 50, who have been without menstrual period for at least 1 year).

8.4.7 Calcitonin

Blood samples for the measurement of calcitonin concentration will be drawn as per flow chart. In case any calcitonin value at any time of the trial is ≥10 ng/L, the algorithm in appendix B should be followed.

8.4.8 Hypoglycaemic episodes

BG should always be measured and recorded when a hypoglycaemic episode is suspected.

All plasma glucose values:

- ≤ 3.9 mmol/L (70 mg/dL) or
- > 3.9 mmol/L (70 mg/dL) when they occur in conjunction with hypoglycaemic symptoms

should be recorded by the subject, except for P10/P10A (see section 8.6.1). These must be transcribed into the eCRF (hypoglycaemic episode form) throughout the trial from visit 1 to phone contact 10.

The record should include the following information:

- Date and time of hypoglycaemic episode
- The plasma glucose level before treating the episode (if available)
- Whether the episode was symptomatic
- Whether the subject was able to treat him/herself
- Date and time and of last trial product administration and other antidiabetic drug(s) administered prior to the episode
- Date and time of last main meal prior to episode
- Whether the episode occurred in relation to physical activity
- Any sign of fever or other disease
- Whether the subject was asleep when the episode occurred
  - If yes, whether the symptoms of the episode woke up the subject

The answer to the question: "Was subject able to treat him/herself?" must be answered "No" for an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.[36]

Oral carbohydrates should not be given if the subject is unconscious.

If the question "Was subject able to treat him/herself?" is answered "No", the following information should be recorded:

- Who assisted in the treatment of the hypoglycaemic episode (i.e. family/friend/co-worker or similar, paramedic, doctor or other, please specify)
- Where the treatment was administered (i.e. at home/at friends/at work or similar, in an ambulance, emergency room/hospital or other, please specify)
- Type of treatment provided by other person (i.e. oral carbohydrates, glucagon, IV glucose or other, please specify)
- Were symptoms alleviated after administration of treatment?

- Factors contributing to the episode (i.e. physical activity, missed meal, diet changed, medication error (i.e. overdose, mix-up between products), other factors not listed, please specify or none)
- Did the subject experience seizure?
- Was the subject unconscious/comatose?
- Did the subject experience any of the following symptoms?[37]
  - Autonomic: sweating, trembling, hunger or palpitations
  - Neuroglycopenic: confusion, drowsiness, speech difficulty, visual disturbances, odd behaviour, impaired balance or incoordination
  - General malaise: headache or malaise
- Did the subject experience other symptoms? Please specify
- Description of the episode, if applicable

A hypoglycaemic episode form must be filled in for each hypoglycaemic episode. If the hypoglycaemic episode fulfils the criteria for an SAE then an AE form and a safety information form must also be filled in, see section 12.

8.5 Laboratory assessments

The laboratory analyses will be performed by a central laboratory. If collected, anti-semaglutide antibody and IgE antibodies will be analysed by Novo Nordisk A/S. The central laboratory may utilise subcontractors. In the events described in section 8.7, a local laboratory must be used. Descriptions of assay methods, laboratory supplies and procedures for collecting, handling, storage and shipping of samples, will be described in the laboratory manual provided by the central laboratory.

Laboratory samples not drawn on the day of the actual visit should preferably be drawn on another day within the visit window stated in the flow chart. For some of the samples drawn during the trial, subjects will be asked to attend the relevant site visits fasting (see section 8.1.5).

Laboratory results will be sent by the central laboratory to the investigator on an on-going basis and the investigator must review all laboratory results for signs of concomitant illness and AEs and report these according to this protocol (see section 12).

The laboratory provides results to the trial sites in the units preferred by the trial sites while the results that are transferred to the trial database will always be in SI units.

The laboratory equipment may provide analyses not requested in the protocol but produced automatically in connection with the requested analyses according to specifications in the laboratory standard operating procedures. Such data will not be transferred to the trial database, but abnormal

values will be reported to the investigator. The investigator must review all laboratory results for concomitant illnesses and AEs and report these according to this protocol.

All laboratory samples will be destroyed at the latest at the completion of the clinical trial report.

8.6 Other assessments

8.6.1 Subject diary

The subject must be provided with paper diaries at visits described in the flow chart. Entries in the diaries are only to be made by the subject, unless otherwise specified.

The investigator should instruct the subject in recording the following data in the diary:

- Date, time and dose of first dose of trial product
- Date and last dose of trial product prior to each visit
- SMPG 7-point profile
- Hypoglycaemic episodes
- Concomitant medication
- AEs

The diaries should be handed out/collected as indicated in the flow chart. The subject should bring the diary for review at every clinic visit during the trial. The recordings must be reviewed as described in section 8.1.8 and transcribed to the eCRF.

Subjects who prematurely discontinue from trial product are not required to use diaries for subsequent scheduled visits after the follow-up premature discontinuation visit (P10A).

If any hypoglycaemic events are reported at P10 or P10A, the information related to the hypoglycaemic event(s) should be documented in the subject's medical record and the entry in the medical record will be considered source data.

8.6.2 Patient reported outcome questionnaires

The following PRO questionnaire will be used in the trial:

- SF-36v2™
- DTSQs

The questionnaires should be completed by the subject, preferably after conclusion of all fasting related activities but before any other visit-related activities. It takes approximately 10 minutes to complete the questionnaires. The assessments must be reviewed as described in section 8.1.8. All results from the PRO questionnaires must be transferred into the eCRF. Please refer to appendix A for details on the PRO questions.

The SF-36v2™ questionnaire will be used to assess subjects overall health related quality of life and can also be used to estimate quality adjusted life years (QALY) which is used in cost effectiveness calculations. This questionnaire contains 36 items and measures the individual overall health related quality of life on 8 domains; physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health.

The DTSQs questionnaire will be used to assess subject's treatment satisfaction. This questionnaire contains 8 items and measures the subject's diabetes treatment (including insulin, tablets and/or diet) in terms of convenience, flexibility and general feelings regarding treatment.

8.6.3 Subject compliance

Throughout the trial, the investigator will remind the subjects to follow the trial procedures and requirements to ensure subject compliance. If a subject is found to be non-compliant, the investigator will remind the subject of the importance of following the instructions given including taking the trial products as prescribed.

Treatment compliance: will be assessed by monitoring of drug accountability. Prior to visits where drug accountability is performed the subject will be asked to return all used, partly used and unused trial products. The investigator must assess the amount of trial products returned compared to what was dispensed at the last dispensing visit and, in case of discrepancies, question the subject.

8.7 Adverse events with additional data collection

For some AEs, additional data collection is required and special forms must be completed in the eCRF, see section 12. The AEs with additional data collection are:

- Cardiovascular events
- Pancreatitis
- Thyroid disease
- Neoplasm
- Hypersensitivity reactions

Selected events (cardiovascular events, pancreatitis, thyroid disease and malignant neoplasm) will be adjudicated and for further details on the definitions, please refer to Table 12–2.

In case any of these events fulfil the criteria for an SAE, this must be reported according to section 12.1.

Acute coronary syndrome

If an event of acute coronary syndrome is observed during the trial, the following information must be reported in the eCRF, if available:

- Duration of symptoms
- Changes in ECG
- Collection of cardiac biomarkers
- Cardiac imaging
- Cardiac stress testing
- Angiography
- Use of thrombolytic drugs
- Coronary Revascularisation procedures

Cerebrovascular events

If a cerebrovascular event is observed during the trial, the following information must be reported in the eCRF, if available:

- Type of event
- Contributing condition
- Neurologic signs and symptoms
- History of neurologic disease
- Imaging supporting the condition
- Treatment given for the condition

Heart failure requiring hospitalisation

If an event of heart failure requiring hospitalisation is observed during the trial, the following information must be reported in the eCRF, if available:

- Signs and symptoms of heart failure
- NYHA Class
- Supportive imaging
- Supportive laboratory measurements
- Initiation or intensification of treatment for this condition

Pancreatitis

In case of a suspicion of acute pancreatitis, the trial product should promptly be interrupted until pancreatitis is ruled out. Appropriate additional examinations must be performed, including local measurement of amylase and lipase.

Appropriate treatment and careful monitoring of the subject should be initiated if pancreatitis is confirmed as a minimum 2 out of the following 3 criteria:

- Severe acute abdominal pain
- Amylase and/or lipase >3x upper normal range (UNR)
- Characteristic findings on relevant imaging e.g. computerised axial tomography (CT)/magnetic resonance imaging (MRI)/ultrasound)

If acute pancreatitis is ruled out, trial product should be re-initiated. If acute pancreatitis is confirmed, the subject must be prematurely discontinued from trial product and should remain in the trial, please refer to sections 6.5 and 8.1.6.

If an event of pancreatitis is observed during the trial, the following information must be reported in the eCRF, if available:

- Signs and symptoms of pancreatitis
- Specific laboratory tests supporting a diagnosis of pancreatitis: amylase, lipase, bilirubin, alkaline phosphatase, ALT and AST
- Imaging performed and consistency with pancreatic disease
- Treatment for and complications of the event
- Relevant risk factors for pancreatic disease including
  - History of gallstones
  - History of pancreatitis
  - Family history of pancreatitis
  - Trauma

Thyroid disease

If an event of thyroid disease, including any thyroid neoplasms observed during the trial, the following information must be reported in the eCRF, if available:

- History of thyroid disease
- Signs and symptoms leading to investigations of thyroid disease
- Specific laboratory tests describing thyroid function: thyroid-stimulating hormone (TSH), calcitonin, thyroid peroxidase antibodies, thyroglobulin and thyroglobulin antibody, TSH receptor antibody, and total and free T3 and T4 and Free Thyroid Index
- Diagnostic imaging performed and any prior imaging supporting the disease history
- Pathologic examinations
- Treatment given for the condition
- Risk factors identified
- Family history of thyroid disease

Neoplasm

All events of neoplasms (excluding thyroid neoplasm, which will be reported under thyroid disease) must be reported during the trial. The following information should be obtained, if available:

- Type of neoplasm
- Symptoms leading to identification of event
- Diagnostic imaging
- Pathological examination results
- Treatment for the event
- Participation in screening programs
- Risk factors associated to the event

Hypersensitivity reactions

In case of suspicion of a hypersensitivity reaction, the subjects should be instructed to contact the trial site staff as soon as possible for further guidance.

All events of hypersensitivity reactions (including allergic reactions, immune complex disease and anti-semaglutide antibody formation) must be reported and the following information must be obtained, if available:

- Signs and symptoms associated with the event
- Time of appearance after administration of trial drug
- Relevant immunological tests performed
- Treatment given for the reaction
- Previous history of similar reactions
- Risk or confounding factors identified

Severe immediate hypersensitivity reaction

In case of suspicion of a severe immediate hypersensitivity reaction to the trial product is suspected, the subject must be prematurely discontinued from trial product and should remain in the trial, please refer to sections 6.5 and 8.1.6.

To assist in diagnosis, it is recommended to draw a blood sample for measurement of tryptase (total and/or mature tryptase, local assessment) within 3 hours of the hypersensitivity reaction, and if this is achieved, a tryptase sample should be collected after a suitable washout period (minimum 5 weeks). Tryptase concentrations should be included in the specific event forms when reporting the AE.

Furthermore, a blood sample for assessment of anti-semaglutide IgE antibodies and anti-semaglutide binding antibodies should be collected after a suitable washout period (minimum 5 weeks).

Immune complex disease

In case of suspicion of immune complex disease, the subject must be prematurely discontinued from trial product and should remain in the trial, please refer to sections 6.5 and 8.1.6. It is recommended to draw a blood sample for local assessment of complement levels (C3 and C4) to assist in diagnosis. Complement level results should be included in the specific event forms when reporting the AE.

9 Trial supplies

Trial supplies comprise trial products and auxiliary supplies. Additional details regarding trial supplies can be found in the Trial Materials Manual.

Trial products must not be dispensed to any person not included in the trial.

Trial products must not be used, if it does not appear clear and colourless.

9.1 Trial products

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

Table 9–1 Trial products

Trial product	Strength	Dosage form	Route of administration	Container/ delivery device
Semaglutide	1.34 mg/mL	Solution for injection	s.c.	PDS290 pen-injector
Dulaglutide	0.75 mg/0.5 mL	Solution for injection	s.c.	Pre-filled pen
Dulaglutide	1.5 mg/0.5 mL	Solution for injection	s.c.	Pre-filled pen

Metformin is considered non-investigational medicinal product and will not be supplied by Novo Nordisk A/S.

Only applicable for Slovakia: All antidiabetic medication will be reimbursed by Novo Nordisk Slovakia s.r.o.

9.2 Labelling

The trial products will be labelled in accordance with Annex 13,[38] local regulations and trial requirements.

Each trial site will be supplied with sufficient trial products for the trial on an on-going basis controlled by the IWRS.

The investigator must document that the DFU is given to the subject orally and in writing at the first dispensing visit (randomisation visit).

9.3 Storage

Table 9–2 Storage of trial products

Trial product	Storage conditions (not-in-use)	In-use conditions	In-use time*
Semaglutide 1.34 mg/mL	Store in refrigerator (2°C-8°C) (US: 36°F-46°F) Do not freeze Protect from light	Store below 30°C (US: 86°F) Do not refrigerate, Do not freeze Protect from light	Use within 1 month
Dulaglutide 0.75 mg/0.5 mL	Store in refrigerator (2°C-8°C) (US: 36°F-46°F) Do not freeze, Protect from light May be stored for up to 12 days not above 30°C (US: 86°F)	N/A (For single use)	N/A (For single use)
Dulaglutide 1.5 mg/0.5 mL	Store in refrigerator (2°C-8°C) (US: 36°F-46°F) Do not freeze, Protect from light May be stored for up to 12 days not above 30°C (US: 86°F)	N/A (For single use)	N/A (For single use)

* In-use time starts when first dose is taken.

The investigator must ensure the availability of proper storage conditions, and also record and evaluate the temperature. The investigator must inform Novo Nordisk **immediately** if any trial product has been stored outside specified conditions (e.g. outside temperature range).

Trial product that has been stored improperly must not be dispensed to any subject before it has been evaluated and approved for further use by Novo Nordisk. The investigator must take appropriate action to ensure correct storage.

9.4 Drug accountability and destruction

Drug accountability is the responsibility of the investigator.

Returned trial product (used/partly used or unused including empty packaging material) can be stored at room temperature and must be stored separately from non-allocated trial product. Drug accountability should be performed at pen level.

Destruction will be done according to local procedures after accountability is finalised and verified by the monitor. Destruction of products must be documented.

9.5 Auxiliary supplies

The following auxiliary supplies will be supplied by Novo Nordisk in accordance with the Trial Materials Manual:

- Needles for PDS290 pen-injector
- DFU for PDS290 pen-injector
- DFU for pre-filled pen
- BG meters and BG meter auxiliaries

10 Interactive web response system

A trial-specific IWRS will be set up which can be accessed at any time via the internet or telephone. Access to the IWRS must be restricted to and controlled by authorised persons.

IWRS is used for:

- Screening
- Screening failure
- Randomisation
- Medication arrival
- Dispensing
- Treatment discontinuation
- Completion
- Drug accountability
- Data change

IWRS user manuals will be provided to each trial site.

11 Randomisation procedure

The trial is an open-label trial. A randomisation session will be performed for all eligible subjects by using the IWRS.

At the randomisation visit, eligible subjects will be randomised to one of the four parallel treatment groups in a 1:1:1:1 manner.

- Semaglutide 0.5 mg/week
- Semaglutide 1.0 mg/week
- Dulaglutide 0.75 mg/week
- Dulaglutide 1.5 mg/week

12 Adverse events, technical complaints and pregnancies

12.1 Definitions

Adverse event

An AE is any untoward medical occurrence in a subject administered a product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product.

An AE includes:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory adverse event (CLAE): a clinical laboratory abnormality which is clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

The following should **not** be reported as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent.
- Non-serious hypoglycaemia is an AE, but is reported on a hypoglycaemic episode form instead of on an AE form, see section 8.4.8.

The following three definitions are used when assessing an AE:

- **Severity**
  - **Mild** - no or transient symptoms, no interference with the subject's daily activities.
  - **Moderate** - marked symptoms, moderate interference with the subject's daily activities.
  - **Severe** - considerable interference with the subject's daily activities; unacceptable.

- **Causality**

Relationship between an AE and the relevant trial product(s):

- **Probable** - Good reason and sufficient documentation to assume a causal relationship.
- **Possible** - A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** - The event is most likely related to aetiology other than the trial product.

- **Final outcome**
  - **Recovered/resolved** - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent.
  - **Recovering/resolving** - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
  - **Recovered/resolved with sequelae** - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
  - **Not recovered/not resolved** - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
  - **Fatal** - This term is only applicable if the subject died from a condition related to the reported AE. Outcomes of other reported AEs in a subject before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
  - **Unknown** - This term is only applicable if the subject is lost to follow-up.

Serious adverse event

A SAE is an experience that at any dose results in any of the following:

- Death.
- A life-threatening[a] experience.
- In-patient hospitalisation[b] or prolongation of existing hospitalisation.
- A persistent or significant disability or incapacity[c].
- A congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening[a] or require hospitalisation[b] may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE[d].

Suspicion of transmission of infectious agents via the trial product must always be considered an SAE.

[a]. The term "life threatening" in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

[b]. The term "hospitalisation" is used when a subject:

- Is admitted to a hospital or in-patient, irrespective of the duration of physical stay, or
- Stays at the hospital for treatment or observation for more than 24 hours

Medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation. Hospitalisations for administrative, trial related and social purposes do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for surgical procedures, planned before trial inclusion, are not considered AEs or SAEs.

[c]. A substantial disruption of a subject's ability to conduct normal life functions (e.g. following the event or clinical investigation the subject has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life).

[d]. For example intensive treatment in an emergency room or at home of allergic bronchospasm, blood dyscrasiasis or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Non-serious adverse event

A non-serious AE is any AE which does not fulfil the definition of an SAE.

Medical event of special interest

A medical event of special interest (MESI) is an event which, in the evaluation of safety, has a special focus as required by health authorities. A MESI is an AE (SAE or non-serious AE) which fulfils one or more of the below defined MESI criteria.

1. Medication errors concerning trial products:
   - Administration of wrong drug or use of wrong device.
     Note: Use of wrong dispensing unit number (DUN) is not considered a medication error unless it results in administration of wrong drug.
   - Wrong route of administration, such as intramuscular instead of s.c.
   - Administration of an overdose with the intention to cause harm (e.g. suicide attempt).
   - Accidental administration of a lower or higher dose than intended. However, the administered dose must deviate from the intended dose to an extent where clinical consequences for the trial subject were likely to happen, as judged by the investigator, although they did not necessarily occur.

Adverse events with additional data collection

AEs with additional data collection are AEs defined as critical for the evaluation of safety. Some of these events will furthermore be adjudicated by an external independent committee as described in section 12.7.2.

The AEs that require additional data collection are listed in Table 12–1 below. For further information about event adjudication and events that require additional data collection, please see sections 12.7.2 and 8.7, respectively.

Table 12–1 Adverse events with additional data collection

Event	Event adjudication	Special eCRF form
Fatal event	Yes	No
Acute coronary syndrome	Yes	Yes
Cerebrovascular event	Yes	Yes
Heart failure requiring hospitalisation	Yes	Yes
Pancreatitis	Yes	Yes
Thyroid disease (including thyroid neoplasm)	Yes (only if thyroid neoplasm or resulting in thyroidectomy)	Yes
Neoplasm (excluding thyroid neoplasm)	Yes (only if malignant)	Yes
Hypersensitivity reactions	No	Yes

Technical complaint

A technical complaint is any written, electronic, or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE, but does not concern the AE itself.

Examples of technical complaints:

- The physical or chemical appearance of trial products (e.g. discoloration, particles or contamination)
- The packaging material (e.g. leakage, cracks, rubber membrane issues or errors in labelling text)
- Problems related to devices (e.g. to the injection mechanism, dose setting mechanism, push button or interface between the pen and the needle)

12.2 Reporting of adverse events

All events meeting the definition of an AE must be collected and reported. This includes events from the first trial-related activity after the subject has signed the informed consent until the end of the post-treatment follow-up period (P10). The events must be recorded in the applicable eCRF forms in a timely manner, see timelines below and Figure 12–1.

During each contact with the trial site staff, the subject must be asked about AEs and technical complaints, for example by asking: "Have you experienced any problems since the last contact?"

All AEs, either observed by the investigator or subject, must be reported by the investigator and evaluated. Novo Nordisk assessment of expectedness is performed according to the following reference documents:

- Semaglutide: NN9535 IB (section 7.3.2) current version[26] and any updates thereto
- Dulaglutide (Trulicity®): Current version of the EU SmPC[28] and U.S. Food and Drug Administration (FDA) prescribing information[29] and any updates thereto

All AEs must be recorded by the investigator on an AE form. The investigator should report the diagnosis, if available. If no diagnosis is available, the investigator should record each sign and symptom as individual AEs using separate AE forms.

For SAEs, a safety information form must be completed in addition to the AE form. If several symptoms or diagnoses occur as part of the same clinical picture, one safety information form can be used to describe all the SAEs.

MESIs, regardless of seriousness, must be reported using both the AE form, the safety information form and a medication error form. The medication error form is a form tailored to collect specific information related to the individual MESI.

AEs with additional data collection must be reported using both AE form and specific additional data collection form. The additional data collection form is a form tailored to collect specific information related to the individual event, see section 8.7

For AEs qualifying for event adjudication, the Event Adjudication form will also have to be completed in the eCRF. The Event Adjudication form is a checklist of clinical data to be provided from the site.

The AE form for a non-serious AE not fulfilling the MESI criteria or additional data collection criteria should be signed when the event is resolved or at the end of the trial.

Timelines for initial reporting of AEs:

The investigator must complete the following forms in the eCRF within the specified timelines:

- **SAEs**: The AE form **within 24 hours** and the safety information form **within 5 calendar** days of the investigator's first knowledge of the SAE. Both forms must be signed within 7 calendar days from the date the information was entered in the eCRF.
- **SAEs fulfilling the MESI criteria:** In addition to above, the medication error form **within 14 calendar days** of the investigator's first knowledge of the AE.
- **SAEs fulfilling criteria for additional data collection:** In addition to above, the corresponding additional data collection form **within 14 calendar days** of investigators first knowledge of the event
- **Non-serious AE fulfilling the MESI criteria:** The AE form, safety information form and medication error form **within 14 calendar days** of the investigator's first knowledge of the event.
- **Non-serious AE fulfilling criteria for additional data collection:** The AE form, and additional data collection form **within 14 calendar days** of the investigators first knowledge of the event
- **AEs for adjudication:** Event Adjudication form should be completed by investigator **within 14 calendar days**. The investigator should provide the medical source documents within 30 days or as soon as possible and on an ongoing basis.

If the eCRF is unavailable, the concerned AE information must be reported on paper forms and sent to Novo Nordisk by fax, e-mail or courier within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the appropriate forms in the eCRF.

Contact details (fax, telephone, e-mail and address) are provided in the investigator trial master file.

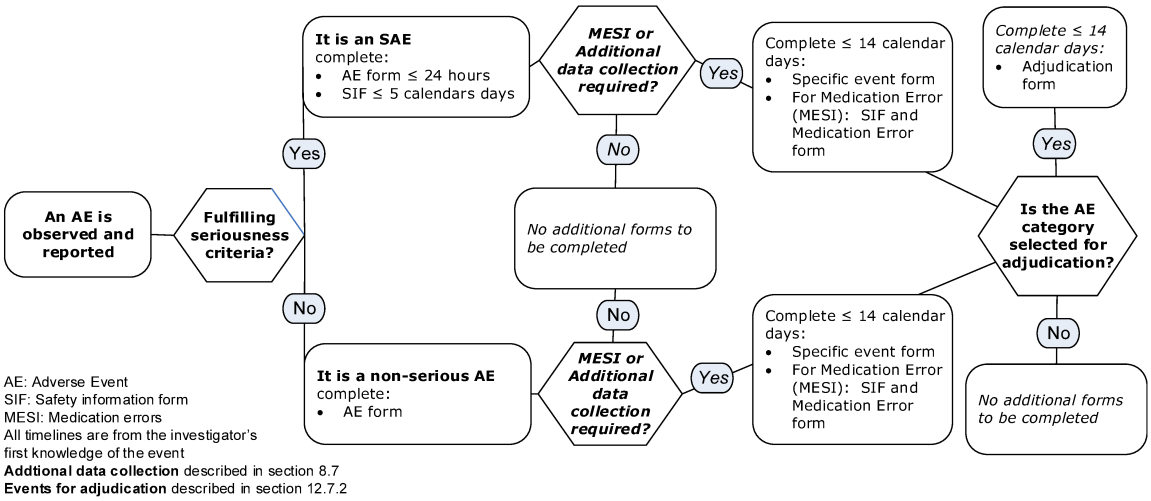


Figure 12–1 Initial reporting of adverse events

Reporting of trial product-related SUSARs by Novo Nordisk:
Novo Nordisk will notify the investigator of trial product-related suspected unexpected serious adverse reactions (SUSARs) in accordance with local requirements and GCP.[1] In addition, the investigator will be informed of any trial-related SAEs that may warrant a change in any trial procedure.

In accordance with regulatory requirements, Novo Nordisk will inform the regulatory authorities, including EMA, of trial product-related SUSARs. In addition, Novo Nordisk will inform the Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) of trial product-related SUSARs in accordance with local requirement and GCP,[1] unless locally this is an obligation of the investigator.

Novo Nordisk products used as concomitant medication:
If a SAE and/or MESI is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the trial, it is important that the suspected relationship is reported to Novo Nordisk, e.g. in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this AE to relevant regulatory authorities.

12.3 Follow-up of adverse events

The investigator must record follow-up information by updating the forms in the eCRF.
Follow up information must be reported to Novo Nordisk according to the following:

- **SAEs**: All SAEs must be followed until the outcome of the event is "recovered/resolved", "recovered/resolved with sequelae" or "fatal", and until all queries have been resolved.

Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.

The SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved" or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the subject has completed the follow-up period and is expected by the investigator to recover.
- **Non-serious AE fulfilling the MESI criteria or additional data collection criteria:** Non-serious AE fulfilling the MESI criteria or additional data collection criteria must be followed as specified for non-serious AEs. Follow-up information on MESIs or AEs with additional data collection should only include new (e.g. corrections or additional) information and must be reported **within 14 calendar days** of the investigator's first knowledge of the information. This is also the case for previously reported non-serious AEs which subsequently fulfil the MESI criteria or the criteria for additional data collection.

The investigator must ensure that the worst case severity and seriousness of an event is kept throughout the trial. A worsening of an unresolved AE must be reported as follow up with re-assessment of severity and/or seriousness of the event.

Queries or follow-up requests from Novo Nordisk must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.4 Technical complaints and technical complaint samples

12.4.1 Reporting of technical complaints

All technical complaints on any of the following products:

- Semaglutide 1.34 mg/mL, solution for injection, 1.5 mL pre-filled PDS290 pen-injector
- Dulaglutide, solution for injection, 0.75 mg/0.5 mL in a pre-filled pen
- Dulaglutide, solution for injection,1.5 mg/0.5 mL in a pre-filled pen
- Novo Nordisk needles for PDS290 pen-injector

which occur from the time of first usage of the product until the time of the last usage of the product, must be collected and reported to Customer Complaint Center, Novo Nordisk.

Contact details (fax, e-mail and address) are provided in Attachment I to the protocol.

The investigator must assess whether the technical complaint is related to any AEs, SAEs, and/or MESI.

Technical complaints must be reported on a separate technical complaint form. A technical complaint form for each batch or lot number or for each DUN must be completed.

The investigator must complete the technical complaint form in the eCRF within the following timelines of the trial site obtaining knowledge of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints within **5 calendar days**

If the eCRF is unavailable or when reporting a technical complaint that is not subject related, the information must be provided on a paper form by fax, e-mail or courier to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF.

12.4.2 Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and notify the monitor **within 5 calendar days** of obtaining the sample at trial site. The monitor must coordinate the shipment to Customer Complaint Center, Novo Nordisk (the address is provided in Attachment I) and ensure that the sample is sent as soon as possible. A print or copy of the technical complaint form must be sent with the sample.

The investigator must ensure that the technical complaint sample contains the batch or lot number and, if available, the DUN.

If the technical complaint sample is unobtainable, the investigator must specify on the technical complaint form why it is unobtainable.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product. The shipment of the technical complaint sample should be done in accordance with the same conditions as for storage (see section 9).

12.5 Pregnancies

12.5.1 Pregnancies in female subjects

Female subjects must be instructed to notify the investigator immediately if they become pregnant during the trial. The investigator must report any pregnancy in subjects who have received trial product(s). In case of pregnancy, the subject must discontinue from trial product, please see sections 6.5 and 8.1.6.

The investigator must follow the pregnancy until the pregnancy outcome and the newborn infant is one month of age.

The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the foetus and newborn infant.

The following must be collected and reported by the investigator to Novo Nordisk - electronically (e.g. in PDF format), or by fax or courier:

1. **Reporting of pregnancy information**
   Information about the pregnancy and pregnancy outcome/health of the newborn infant(s) has to be reported on Maternal Form 1A and 1B, respectively.

   When the pregnancy outcome is abnormal (i.e. congenital anomalies, foetal death including spontaneous abortion and/or any anomalies of the foetus observed at gross examination or during autopsy), and/or when a congenital anomaly is diagnosed within the first month, further information has to be reported for the female subject on Maternal Form 2. In addition, information from the male partner has to be reported on the Paternal Form, after an informed consent has been obtained from the male partner.

   Initial reporting and follow-up information must be reported **within 14 calendar days** of the investigator's first knowledge of initial or follow-up information.

2. **Reporting of AE information**
   The investigator has to report AEs in connection with the pregnancy as well as in the foetus and newborn infant(s). The SAEs that must be reported include abnormal outcome, such as foetal death (including spontaneous abortion), and congenital anomalies (including those observed at gross examination or during autopsy of the foetus), as well as other pregnancy complications fulfilling the criteria of an SAE.

Forms and timelines for reporting AEs:

Non-serious AEs:

- Paper AE form* **within 14 calendar days** of the investigator's first knowledge of the initial or follow-up information to the non-serious AE.

SAEs:

- Paper AE form* **within 24 hours** of the investigator's first knowledge of the SAE.
- Paper safety information form **within 5 calendar days** of the investigator's first knowledge of the SAE.
- **SAE follow-up information** to the AE form and/or safety information form **within 24 hours** of the investigator's first knowledge of the follow-up information.

* It must be clearly stated in the AE diagnosis field on the AE form if the event occurred in the subject, foetus or newborn infant.

Any queries or follow-up requests from Novo Nordisk to non-serious AEs, SAEs and pregnancy forms must be responded to by the investigator **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

12.6 Precautions and/or overdose

Semaglutide: Events of nausea, vomiting and headache have been reported in connection with accidental administration of semaglutide doses up to 4 mg. No symptoms of hypoglycaemia have been reported in connection with overdose of semaglutide. In the event of overdosage, appropriate supportive treatment should be initiated according to subject’s clinical signs and symptoms

Dulaglutide: Overdoses have been reported in clinical studies. Effects associated with these overdoses were primarily mild or moderate gastrointestinal events (e.g., nausea, vomiting) and non-severe hypoglycaemia. In the event of overdose, appropriate supportive care (including frequent plasma glucose monitoring) should be initiated according to the subject’s clinical signs and symptoms.

12.7 Committees related to safety

12.7.1 Novo Nordisk safety committee

Novo Nordisk will constitute an internal semaglutide safety committee to perform ongoing safety surveillance as well as surveillance of laboratory safety data. The semaglutide safety committee may recommend unblinding of any data from the NN9535 and NN9536 semaglutide for obesity programmes for further analysis, and in this case an independent ad hoc group will be established in order to maintain the blinding of the trial personnel.

12.7.2 Event adjudication committee

An independent external event adjudication committee (EAC) is established to perform qualitative or quantitative validation of selected AEs according to pre-defined diagnostic criteria. The validation is based on review of pre-defined clinical data related to the specific AE. Pre-defined clinical data consist of copies of source documents collected and delivered by the trial sites.

The EAC is composed of permanent members covering required medical specialities. EAC members must disclose potential conflicts of interest and must be independent of Novo Nordisk.

The events are reviewed by the EAC in a blinded manner. The EAC will have no authorisations to impact on trial conduct, trial protocol or amendments.

The EAC works in accordance with written guidelines included in the EAC Charter describing in details the composition, tasks, responsibilities and work processes of the committee.

The events outlined in Table 12–2 have been selected for adjudication in order to obtain an external independent validation of the diagnosis. In addition, cardiovascular events are being adjudicated according to FDA requirements.

The EAC will review copies in English (translated if necessary) of medical documentation received in the adjudication packages (e.g. x-ray, ECGs, ultrasound images, discharge summaries, pathology reports and death certificates). The investigator must provide medical documentation as soon as possible, when they receive the request from Novo Nordisk or the Event Adjudication Vendor.

The assessments made by the EAC will be included in the clinical trial report as well as assessments made by the investigator. However, the adjudication made by an EAC, given its independence and in-depth analysis of each event, will be attributed with greater importance of the two. The outcome of adjudication will be kept in the clinical trial database.

The following AEs will be adjudicated in this trial:

Table 12–2 Adverse events for adjudication

Event	Definition
Fatal event	All cause mortality: • Cardiovascular death, • Non-cardiovascular death, • Undetermined cause of death
Acute coronary syndrome	All types of MI must be reported: • Spontaneous MI (including re-infarction and MI associated with stent thrombosis) • Percutaneous coronary intervention (PCI) related MI • Coronary artery bypass graft surgery (CABG) related MI • Silent MI All events with symptoms of myocardial ischaemia requiring hospitalisation must be reported.
Cerebrovascular event	TIA: TIA is defined as a transient (<24 hours) episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischaemia, without acute infarction. Stroke (ischaemic, haemorrhagic, undetermined) : Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction.
Heart failure requiring hospitalisation	Clinical manifestations of new episode or worsening of existing heart failure.
Pancreatitis	Two of following diagnostic criteria fulfilling the diagnosis of acute pancreatitis: • Severe acute abdominal pain • Elevated blood levels of pancreatic enzymes (lipase, amylase) > 3xUNR • Characteristic imaging finding (e.g. by ultrasound, CT, MRI) Chronic pancreatitis will be defined by characteristic imaging finding (e.g. by ultrasound, CT, MRI) with abnormal pancreatic function tests or characteristic histological findings
Thyroid diseases, if thyroid neoplasm or resulting in thyroidectomya	All thyroid diseases requiring thyroidectomy, including partial thyroidectomy (e.g. lobectomy, partial lobectomy and biopsies) will be adjudicated. All thyroid neoplasms will be adjudicated.
Malignant neoplasm	Malignant neoplasms, defined as neoplasms in which abnormal cells divide without control and can invade nearby tissues and/or spread to other parts of the body through the blood and lymph systems. Note: For operational reasons thyroid neoplasm will be reported as a thyroid disease.

All AEs will be screened for potential missed events for adjudication and if needed, the investigator will be asked to provide additional information such as an alternative aetiology, underlying cause(s) and/or clinical details.

The adjudication vendor or EAC can decide to have an AE adjudicated even if not initially reported as an event for adjudication by the investigator.

Event adjudication will be performed for AEs in randomised subjects including AEs with an onset date during the screening period. Event adjudication will not be performed for AEs in screening failures.

AEs for adjudication must be reported according to section 12.2. In addition, the specific adjudication document collection form should be completed within 14 calendar days of the investigator's first knowledge of the AE, and all relevant predefined documents provided according to instructions in the event adjudication site manual.

13 Case report forms

Novo Nordisk will provide a system for the eCRF. This system and support services to the system will be provided by an external supplier.

Ensure that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g. is not applicable), indicate this according to the data entry instructions.

The following will be provided as paper CRFs:

- Pregnancy forms

In addition paper AE forms, technical complaint forms and safety information forms will be provided. These must be used when access to the eCRF is revoked or if the eCRF is unavailable.

On the paper CRF forms print legibly, using a ballpoint pen. Ensure that all questions are answered, and that no empty data blocks exist. Ensure that no information is recorded outside the data blocks. If a test/assessment has not been done and will not be available, indicate this by writing "ND" (not done) in the appropriate answer field in the CRF. If the question is irrelevant (e.g. is not applicable) indicate this by writing "NA" (not applicable) in the appropriate answer field. Further guidance can be obtained from the instructions in the CRF.

The investigator must ensure that all information is consistent with the source documentation. By electronically signing the case book in the eCRF, the investigator confirms that the information in the eCRF and related forms is complete and correct.

13.1 Corrections to case report forms

Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction.

If corrections are made by the investigator's delegated staff after the date the investigator has signed the case book, the case book must be signed and dated again by the investigator.

13.2 Case report form flow

The investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

The pregnancy forms are paper based CRFs. Also, the AE forms, technical complaint forms, and safety information forms will be provided in paper but are only to be used if for any reason the eCRF is unavailable.

The investigator must ensure that data is recorded in these forms as soon as possible after the visit.

At the end of the trial the investigator must ensure that all remaining data have been entered into the eCRF no later than 3 days after LPLV at the site in order to ensure the planned lock of the database.

Site specific eCRF data (in an electronic readable format) will be provided to the trial site before access to the eCRF is revoked. This data must be retained at the trial site.

14 Monitoring procedures

During the course of the trial, the monitor will visit the trial site to ensure that the protocol is adhered to, that all issues have been recorded, to perform source data verification and to monitor drug accountability. The first monitoring visit will be performed as soon as possible after FPFV at the trial site and no later than 4 weeks after. The monitoring visit intervals will depend on the outcome of the remote monitoring of the CRFs, the trial site's recruitment rate and the compliance of the trial site to the protocol and GCP, but will not exceed 12 weeks for trial sites with active subjects (defined as subjects in screening, treatment or follow-up).

The monitor must be given direct access to source documents (original documents, data and records). Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition the relevant trial site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

All data must be verifiable in source documentation other than the CRF.

For all data recorded the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data element.

Source data generated by the trial site can be corrected by another person than the person entering the source data if accepted by local regulations; any correction must be explained, signed and dated by the person making the correction.

The original diaries and PROs must not be removed from the trial site, unless they form part of the CRF and a copy is kept at the site.

The monitor will ensure that the eCRFs are completed and that paper CRFs are collected.

The following data will be source data verified for screening failures:

- Date for obtaining informed consent
- Reason for screen failure

Monitors must review the subject's medical records and other source data (e.g. the diaries and PROs) to ensure consistency and/or identify omissions compared to the CRF. If discrepancies are found, the investigator must be questioned about these.

A follow-up letter (paper or electronic) will be sent to the investigator following each monitoring visit. This should address any action to be taken.

15 Data management

Data management is the responsibility of Novo Nordisk. Data management may be delegated under an agreement of transfer of responsibilities to a contract research organisation.

Appropriate measures, including encryption of data files containing person identifiable data, will be used to ensure confidentiality of subject data, when they are transmitted over open networks.

Data from central laboratories will be transferred electronically. In cases where data is transferred via non-secure electronic networks, data will be encrypted during transfer.

The subject and any biological material obtained from the subject will be identified by subject number and trial ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of subjects in all presentations and publications as required by local, regional and national requirements.

In cases where data management activities are delegated to external vendors, there will be regular transfers of data during the trial.

16 Computerised systems

Novo Nordisk will capture and process clinical data using computerised systems that are described in Novo Nordisk Standard Operating Procedures and IT architecture documentation. The use and control of these systems are documented.

Investigators working on the trial may use their own electronic systems to capture source data.

17 Statistical considerations

General considerations

No interim analyses or other analyses of unmasked or between group data will be performed before the database is locked.

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

Data from all trial sites will be analysed and reported together.

If an assessment has been made both at screening and randomisation, and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If an assessment is missing at randomisation, but available at screening, then the screening value will be used as the baseline value.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

Results from a statistical analysis will be presented by the estimated treatment contrasts at week 40 with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference if not otherwise specified.

The two principal comparisons presented from a statistical analysis are

- s.c. semaglutide 0.5 mg versus dulaglutide 0.75 mg
- s.c. semaglutide 1.0 mg versus dulaglutide 1.5 mg

Primary estimand

The primary objective of the trial is to compare the effect of once-weekly dosing of two dose levels of s.c. semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of each of the two dose levels of s.c. dulaglutide (0.75 mg and 1.5 mg) on glycaemic control in subjects with T2D on a background treatment with metformin.

The primary estimand will be:

- de-jure treatment difference at week 40 for all randomised subjects if all subjects adhered to treatment and did not initiate antidiabetic rescue medication

This estimand assesses the glycaemic benefit a future subject is expected to achieve if he/she initiates and continue treatment with s.c. semaglutide as compared to dulaglutide. It is considered a

clinically relevant estimand as it provides information to treating clinicians about the expected glycaemic efficacy of s.c. semaglutide for purposes of treating individual subjects with T2D.

Missing data considerations

Since both semaglutide and dulaglutide are GLP-1 RA, it is reasonable to assume that missing data in both arms will be similar in timing, extent and reason. Based on the phase 2 semaglutide dose-finding trial (NN9535-1821) and the slower dose escalation implemented in this trial, the rate of discontinuing treatment prematurely or initiating rescue medication on top of trial product is expected to be maximum 25% and similar across treatment arms after 40 weeks of treatment.

Since efficacy for both semaglutide and dulaglutide have been shown, missing data due to ineffective therapy is not anticipated to be a notable issue. However, some missing data due to AEs is expected in both treatment arms because of gastrointestinal related AEs leading to premature treatment discontinuation primarily during initiation and dose escalation.

Descriptive summaries and graphical representation of extent, reason(s) for and pattern of missing data will be presented by treatment arm.

17.1 Sample size calculation

The primary endpoint is change from baseline in HbA_{1c} after 40 weeks of treatment. For HbA_{1c}, both non-inferiority and subsequently superiority are planned to be tested at each dose level (semaglutide 0.5 mg versus dulaglutide 0.75 mg and semaglutide 1.0 mg versus dulaglutide 1.5 mg). The confirmatory secondary endpoint is change from baseline in body weight after 40 weeks of treatment. For body weight, superiority is planned to be tested at each dose level.

The sample size calculation is based on jointly meeting four out of the six pre-specified confirmatory hypotheses shown in Figure 17–1. The closed testing procedure described in Bretz et al[39] is used to control the overall type-1 error at a nominal two-sided 5% level. The four hypotheses are:

- HbA_{1c} non-inferiority of semaglutide 0.5 mg versus dulaglutide 0.75 mg (margin of 0.4%)
- Body weight superiority of semaglutide 0.5 mg versus dulaglutide 0.75 mg
- HbA_{1c} non-inferiority of semaglutide 1.0 mg versus dulaglutide 1.5 mg (margin of 0.4%)
- Body weight superiority of semaglutide 1.0 mg versus dulaglutide 1.5 mg

The sample size is calculated using the calcPower function in the R package, gMCP[40] using 10000 simulations. All of the six pre-specified confirmatory hypotheses are assumed to be independent. Since positive correlations are expected, the assumption of independence is viewed as conservative.

Furthermore, the sample size calculation is based on the following assumptions:

Based on the phase 2 s.c. semaglutide dose-finding trial (NN9535-1821), the standard deviation for HbA_{1c} is assumed to be 1.1% and the standard deviation for body weight is assumed to be 4 kg.

The assumed treatment difference in HbA_{1c} of semaglutide relative to dulaglutide at week 40 within both dose levels is zero. The assumed treatment difference in body weight of semaglutide relative to dulaglutide at week 40 within both dose levels is 1.5 kg. A 50% smaller effect on body weight is assumed in the 25% of subjects expected to discontinue treatment prematurely or initiate rescue medication on top of trial product. This leads to an adjusted treatment effect of 1.35 kg for body weight, which is the value used in the sample size calculation. Based on oral semaglutide phase 2 results (NN9924-3790), the 50% efficacy retention is viewed as conservative in light of the primary analysis but less so for the in-trial sensitivity analyses that uses all data collected during the trial.

With the above assumptions, allocating 299 subjects to each of the semaglutide and dulaglutide arms yields 90% power to confirm HbA_{1c} non-inferiority and body weight superiority between semaglutide and dulaglutide at both dose levels.

Calculated powers for selected individual hypotheses are presented in Table 17–1. In total 4×299 = 1196 subjects are planned to be randomised.

Table 17–1 Calculated powers for individual hypotheses

Statistical test	HbA_{1c} non-inferiority (margin=0.40%)		Body weight superiority		HbA_{1c} superiority	
Treatment dose level	High	Low	High	Low	High	Low
Power (%)	99	99	95	95	1.2	1.2

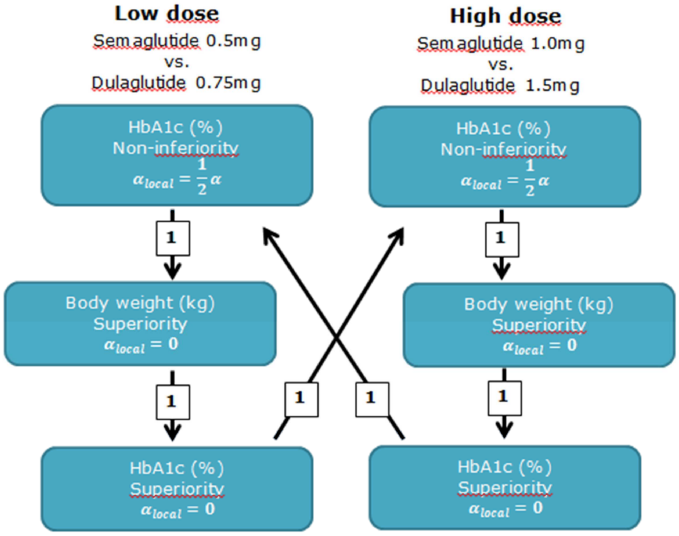


Figure 17–1 Graphical illustration of the closed testing procedure

The Type-I error for the six pre-specified confirmatory hypotheses will be controlled in the strong sense using the closed testing procedure in Figure 17–1. The initial allocation of the overall significance level of α=0.05 (two-sided) is split equally between non-inferiority at the two dose levels. The local significance level (α_{local}) will be reallocated if a hypothesis is confirmed according to the weight given by directed edge between nodes (the hypotheses).

17.2 Definition of analysis sets

The following analysis sets will be defined:

Full analysis set (FAS): includes all randomised subjects exposed to at least one dose of trial product. Subjects in the FAS will contribute to the evaluation "as randomised".

Safety analysis set (SAS): includes all randomised subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation "as treated".

Per protocol (PP) analysis set: includes all subjects in the FAS who fulfil the following criteria:

- Have not violated any inclusion criteria
- Have not fulfilled any exclusion criteria
- Have a non-missing HbA_{1c} measurement at screening and/or randomisation
- Is on trial product at week 28 and have at least one non-missing HbA_{1c} measurement at or after week 28

Subjects in the PP analysis set will contribute to the analysis "as treated".

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion will be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

Data selections and observations periods

Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial, which is until the follow-up phone contact (P10).

The data to be used in all analyses will be selected in two steps.

Step 1: The subjects and treatment principle (as treated or as randomised) to be used in the analysis will be selected based on the specified *analysis set.*

Step 2: Data points for subjects used in the analysis set will be selected according to whether or not the data points belongs to the specified *observation period* (In-trial, on-treatment or on-treatment without rescue as defined below). Information collected with onset date outside the observation period will be treated as missing and therefore excluded from the corresponding analysis. For adjudicated events, onset date will be the EAC adjudicated onset date.

- ***In-trial:*** The in-trial observation period includes observations recorded at or after randomisation (as registered in IWRS) and not after the last subject-investigator contact, which is scheduled to take place 5 weeks after planned last dose of trial product at a follow-up phone contact (P10). For subjects who withdraw their informed consent, the in-trial observation period ends at their date of withdrawal. In the case a subject dies during the trial, the date of death will be the end-date of the in-trial observation period. If a subject is lost to follow-up, the end of his/her in-trial period is defined as the date of the last subject-investigator contact (site or phone visit). Analysis based on this observation period includes data regardless of treatment exposure and/or usage of non-investigational antidiabetic medications. Since non-investigational antidiabetic medications can mask or exaggerate both the efficacy and safety effects, this observation period will be in line with the primary estimand and is considered supportive for both efficacy and safety evaluations.
- ***On-treatment:*** This observation period represents the time period where subjects are considered treated with trial product. The observation period is a subset of the in-trial observation period and two slightly different data handling rules will be needed to cover all assessments appropriately. For adjudicated events, ECGs and AEs including hypoglycaemic episodes, this observation period will represent information collected while subjects are

considered exposed to trial product. This corresponds to information collected up until the follow-up phone contact, which is scheduled to take place 5 weeks after premature treatment discontinuation to reflect five half-lives of s.c. semaglutide including a visit window of +7 days. For the remaining safety and efficacy assessments that are collected up until and not after the end of treatment visit, the follow-up period will not be included in the on-treatment observation period. In line with the primary estimand, the on-treatment observation period will be the primary observation period used in safety evaluations and considered supportive of efficacy evaluations.

- ***On-treatment without rescue:*** This observation period is a subset of the on-treatment observation period, where subjects do not receive any non-investigational antidiabetic medication (rescue medication). Specifically it includes observations recorded at or after date of first dose of trial product and not after the first occurrence of the following:
    - The last dose of trial product plus the dosing interval
    - Initiation of rescue medication

For subjects who have no post-baseline scheduled assessments available in the on-treatment without rescue period, the baseline value will be carried forward to the first scheduled visit for the associated endpoint to ensure that all randomised subjects will contribute to the statistical analysis. In line with the primary estimand, the on-treatment without rescue observation period will be the primary observation period used in efficacy evaluations.

17.3 Primary endpoint

The primary analysis used to estimate the primary estimand will be based on FAS using data from the on-treatment without rescue observation period in a Mixed Model for Repeated Measures (MMRM). A restricted maximum likelihood (REML) will be used. The model will include all post baseline HbA_{1c} measurements collected at scheduled visits up to and including week 40 data as dependent variables. The independent effects included in the model will be treatment and country as fixed effects and baseline response as covariate, all nested within visit. An unstructured covariance matrix will be employed for measurements within the same subject, assuming that measurements across subjects are independent. From this model, the two by dose level estimated treatment differences between s.c. semaglutide versus dulaglutide at week 40 will be presented together with associated two-sided 95% confidence intervals and unadjusted two sided p-values (nominal alpha=0.05) for testing non-inferiority and superiority.

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. This analysis assumes that the missing data mechanism is missing at random (MAR). Thus, for a subject who has missing data, MAR assumes a value for the endpoint based on observed data of subjects whose baseline explanatory variables and response up to withdrawal are similar to that of the discontinued subject. Since there is no historical evidence suggesting that subjects

discontinuing semaglutide prematurely have better outcome on average than those who remain on treatment, the primary analysis is not expected to bias the estimated HbA_{1c} treatment effect for the primary estimand in favour of semaglutide to any important degree. This is based on the s.c. semaglutide phase 2 (NN9535-1821) results and further supported by data from liraglutide clinical trials.

Hypotheses tested for the primary endpoint

For HbA_{1c}, the following two confirmatory hypotheses are planned to be tested at each dose level comparing; (i) semaglutide 0.5 mg versus dulaglutide 0.75 mg and (ii) semaglutide 1.0 mg versus dulaglutide 1.5 mg with mean treatment difference defined as μ=(semaglutide minus dulaglutide):

- Non-inferiority using a non-inferiority margin of 0.4
  - H_0: μ>=0.4% against Ha: μ <0.4%

- Superiority
  - H_0: μ>=0.0% against Ha: μ<0.0%

Operationally, the hypotheses will be assessed using two-sided p-values.

Multiplicity and criteria for confirming hypotheses

The Type-I error for testing the six confirmatory hypotheses related to HbA_{1c} and body weight endpoints will be preserved in the strong sense at 5% (two-sided) using the weighted Bonferroni-based closed testing procedure described in Bretz et al[39] and outlined in Figure 17–1. First the 2 non-inferiority hypotheses at each dose level will be tested each at its initial allocated local significance level of 0.025%. If a non-inferiority hypothesis is confirmed, the local significance level will be reallocated according to the edge going out of the confirmed hypothesis as specified in Figure 17–1. Each of the following hypotheses will be tested at their local significance level (α-local). This process will be repeated until no further hypothesis can be confirmed.

Non-inferiority and/or superiority will be considered confirmed if the mean treatment difference is supporting the corresponding hypothesis and the two-sided p-value (nominal alpha=0.05) is strictly below its local two-sided significance level as defined by the closed testing procedure in Figure 17–1. This is equivalent to using a one-sided p-value (nominal alpha=0.025) and a one-sided 2.5% overall significance level in the closed testing procedure.

Sensitivity analyses

The aim of the below pre-specified sensitivity analyses is to explore the impact of departures from the missing data assumption made in the primary analysis of HbA_{1c} and the confirmatory secondary analysis of body weight (see section 17.4.1). This is consistent with European Medicines Agency (EMA) recommendations[41] and with a report from the US National Research Council.[42] Since

conservatism (i.e. avoiding bias in favour of semaglutide) depends on the context, the sensitivity analyses are targeted to whether non-inferiority or superiority is being tested.

Pattern-mixture model using multiple imputation addressing both non-inferiority and superiority
The below pattern-mixture model based sensitivity analyses imputes missing data in a way that is likely to be less favourable for s.c. semaglutide as compared to the primary HbA_{1c} analysis. The multiple imputation sensitivity analysis stress-tests the primary HbA_{1c} conclusions by changing the missing data assumptions about s.c. semaglutide, while using the MAR assumption for subjects randomised to dulaglutide.

- *Comparator multiple imputation analysis* - In this analysis, all monotone missing data for subjects randomised to s.c. semaglutide 1.0 mg are imputed to have HbA_{1c} response trajectory statistically similar to subjects treated with dulaglutide 1.5 mg and for subjects randomised to s.c. semaglutide 0.5 mg are imputed to resemble in distribution subjects treated with dulaglutide 0.75 mg. The analysis will be based on the FAS using the on-treatment without rescue observation period. A sequential multiple imputation modelling approach by dose level will be implemented in which all observed post-baseline dulaglutide data are used to impute all monotone missing values. As a preliminary step, non-monotone or intermediate missing data will be imputed by treatment using a Markov Chain Monte Carlo method under the assumption of MAR and a multivariate normal distribution over baseline and scheduled post baseline measurements. For non-inferiority testing an additional step is included. Here all the imputed values in a s.c. semaglutide treatment arm are made worse by the non-inferiority margin at week 40. This is based on the assumption that missing values for subjects randomised to s.c. semaglutide will be imputed according to a treatment expected inferior to dulaglutide in order to ensure that non-inferiority is not unduly favoured.

Sensitivity analyses addressing non-inferiority
In support of non-inferiority testing, the below two sensitivity analyses will be performed. These sensitivity analyses only include a subset of all randomised subjects so the integrity of randomisation may not be maintained. Therefore, while the below two analyses generally are conservative for testing non-inferiority, the inherent risk for bias in any direction cannot be excluded.

- *PP analysis* – the statistical analysis will be the same as the primary MMRM based analysis but it will be based on the PP analysis set and the on-treatment without rescue observation period.
- *Complete case analysis* – includes subjects in the FAS who do not have their endpoint imputed in the primary analysis. The change from baseline in HbA_{1c} at week 40 will be analysed by a linear normal model (analysis of covariance (ANCOVA)) with treatment and country as fixed effects and baseline HbA_{1c} as a covariate.

Other sensitivity analyses

The following secondary estimand will be defined:

- de-facto treatment difference at week 40 for all randomised subjects

This estimand assesses the average effect in a future population that results from treatment with s.c. semaglutide plus antidiabetic rescue medication(s) as compared to treatment with dulaglutide plus antidiabetic rescue medication(s). Interpretation of this estimand depends on whether the use of antidiabetic rescue medication and treatment adherence in this trial reflects clinical practice. The de-facto estimand will be estimated from the below analysis:

- *In-trial analysis* – This analysis will be based on the FAS using the in-trial observation period. The statistical analysis will be the same as the primary MMRM based analysis. The MAR assumption is considered a reasonable approach for handling missing data, as the two trial products can be considered to have efficacy similar to standard of care treatment available for treatment of T2D. This analysis will also be considered as a sensitivity analysis for evaluating the robustness of the primary analysis.

The last sensitivity analysis will be:

- *Last observation carried forward (LOCF) analysis* – This analysis will be based on the FAS using the on-treatment without rescue observation period with missing data imputed by LOCF. Based on the complete data set, the change from baseline in HbA_{1c} at week 40 will be analysed by a linear normal model (ANCOVA) with treatment and country as fixed effects and baseline HbA_{1c} as a covariate.

Assessment of sensitivity analyses

The results from the sensitivity analysis will be collectively used to interpret the confirmatory trial conclusions on HbA_{1c} and body weight, and in particular evaluate the impact of the MAR assumptions. No absolute criteria will be defined as to when a sensitivity analysis can be defined to have confirmed the robustness of the conclusions. Due to the large number of the sensitivity analyses and their inherent conservative nature, it is not considered a requirement that all confirmatory hypotheses are confirmed across all the sensitivity analyses. The results of the sensitivity analysis will be discussed in the clinical trial report with the aim to use the sensitivity results in totality to evaluate the credibility of the confirmatory trial conclusions.

17.4 Secondary endpoints

17.4.1 Confirmatory secondary endpoint

The confirmatory secondary endpoint is change from baseline to week 40 in body weight (kg). This endpoint will be analysed in the same type of model as the primary endpoint, except with baseline body weight as a covariate instead of baseline HbA_{1c}. From this model the two by dose level estimated treatment differences between semaglutide versus dulaglutide will be presented at week 40 together with associated two-sided 95% confidence intervals and unadjusted two sided p-values (nominal alpha=0.05). The same sensitivity analyses as pre-specified for testing superiority for the primary HbA_{1c} endpoint will also be performed to evaluate the robustness of the body weight superiority conclusions.

Confirmatory secondary hypothesis
For body weight, the following confirmatory hypothesis will be tested at each dose level comparing; (i) semaglutide 0.5 mg versus dulaglutide 0.75 mg and (ii) semaglutide 1.0 mg versus dulaglutide 1.5 mg with mean treatment difference defined as μ=(semaglutide minus dulaglutide):

- Superiority
  - H_0: μ >=0.0% against Ha: μ <0.0%

Superiority will be considered confirmed if the corresponding two-sided p-value (nominal alpha=0.05) is strictly below its local two-sided significance level as defined by the closed testing procedure in Figure 17–1.

17.4.2 Supportive secondary endpoints

17.4.2.1 Efficacy endpoints

The supportive secondary efficacy endpoints will be presented based on FAS using the on-treatment without rescue observation period as the key observation period with the in-trial observation period being supportive.

Endpoints include change from baseline to week 40 in:

- FPG*
- SMPG, 7-point profile:
  - Mean 7-point profile, defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time
  - Mean post prandial increment (over all meals)

- Fasting blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)
- BMI and waist circumference
- Systolic and diastolic blood pressure*
- Patient reported outcomes
  - SF-36v2™
  - DTSQ*

The above continuous endpoints will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as a covariate. Fasting blood lipids profile endpoints will be log-transformed prior to analysis including also the relevant log-transformed baseline value used as a covariate.

Subjects who after 40 weeks treatment achieve (yes/no)

- HbA_{1c} <7.0% (53 mmol/mol) ADA target
- HbA_{1c} ≤6.5% (48 mmol/mol) AACE target*
- Weight loss ≥5%
- Weight loss ≥10%
- HbA_{1c} <7.0% (53 mmol/mol) without severe or BG confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA_{1c} reduction ≥1%
- Weight loss ≥3%
- HbA_{1c} reduction ≥1% and weight loss ≥3%

The above eight binary endpoints will be analysed using a logistic regression model with treatment and region as fixed effects and baseline response as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c} endpoints, baseline weight for weight endpoints and both baseline HbA_{1c} and baseline weight for the binary endpoint that combines both parameters). To account for missing data, the analysis will be made using a sequential multiple imputation approach as described below:

- Multiple imputed data sets (100) will be created in which missing values for the underlying continuous assessments are imputed by treatment group assuming MAR and as described in section 17.3.
- The binary endpoint will be created for each of the 100 complete data sets
- Each of the created complete data set will be analysed with the logistic model and inference will be drawn using Rubin's rule.[43]

PRO outcomes

The PRO outcomes endpoints that will be analysed at week 40 are:

- PRO questionnaire outcome DTSQs (individual items and treatment satisfaction score (6 of the 8 items summed)), and
- PRO questionnaire outcome SF-36v2™

The above continuous endpoints will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as a covariate.

7-point profile (SMPG)

Subjects will be asked to perform SMPG measurements before and 90 minutes after breakfast, lunch, dinner, respectively, and at bedtime.

The endpoints from the 7-point profiles that will be analysed at week 40 are:

- Mean of the 7-point profile, defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time
- Mean increment over all meals

The mean of the 7-point profile and the mean of the post prandial increments at week 40 will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as a covariate.

17.4.2.2 Safety endpoints

All safety endpoints will be evaluated based on SAS and the on-treatment observation period as the primary observation period with the in-trial observation period being supportive if not otherwise specified.

The following endpoints are used to support the safety objectives:

- Number of TEAEs
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemia episodes
- Treatment emergent severe or BG confirmed symptomatic hypoglycaemia (yes/no)

Change from baseline to week 40 in:

- Lipase
- Amylase
- Pulse

The above continuous endpoints will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as covariate. Lipase and amylase endpoints will be log-transformed prior to analysis including also the relevant log-transformed baseline value as covariate.

The following laboratory assessments will be summarised descriptively:

- Haematology
- Biochemistry
- Calcitonin

The following categorical safety evaluations will be summarised descriptively:

- ECG category
- Physical examination

Calcitonin

In addition to the continuous summaries, calcitonin will be displayed in terms of the number of subjects (N), the percentage of subjects (%) and the event rate per 100 years of exposure (R). The below criteria are defined for categorical tabulations. Summaries will be presented for all subjects and by gender.

- Persistent (all post baseline measurements)
- From < upper normal limit (UNL) to persistently ≥ UNL
- From <UNL to persistently ≥1.5 UNL
- From <UNL to persistently ≥20 ng/L
- From <UNL to persistently ≥50 ng/L
- From <20 ng/L to persistently ≥20 ng/L
- From <50 ng/L to persistently ≥50 ng/L

Adverse Events

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

A TEAE is defined as an AE with onset in the on-treatment period (see definition of observation period in section 17.2).

TEAEs will be summarised in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 patient years of observation time (R) for the on-treatment observation period. Supportive summaries of AEs will be made for the in-trial observation period.

Classification of Hypoglycaemia:

Hypoglycaemic episodes will be summarised for the SAS and the on-treatment observation period. No supportive summaries will be made based on the in-trial observation period and episodes with onset date after the on-treatment observation period will be reported in listings only.

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset is in the on-treatment period (see definition of observation period in section 17.2)

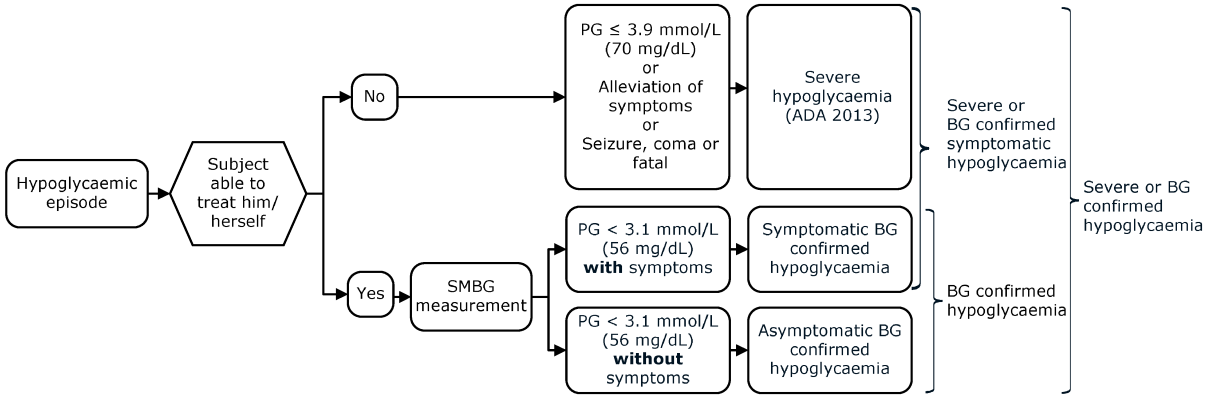
Nocturnal hypoglycaemic episodes: are episodes occurring between 00:01 and 05.59 both inclusive.

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 17–2) and the ADA classification of hypoglycaemia (see Figure 17–3).

Novo Nordisk classification of hypoglycaemia
In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL).[44] Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 17–2) in addition to the ADA classification:

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[36] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) **with** symptoms consistent with hypoglycaemia.

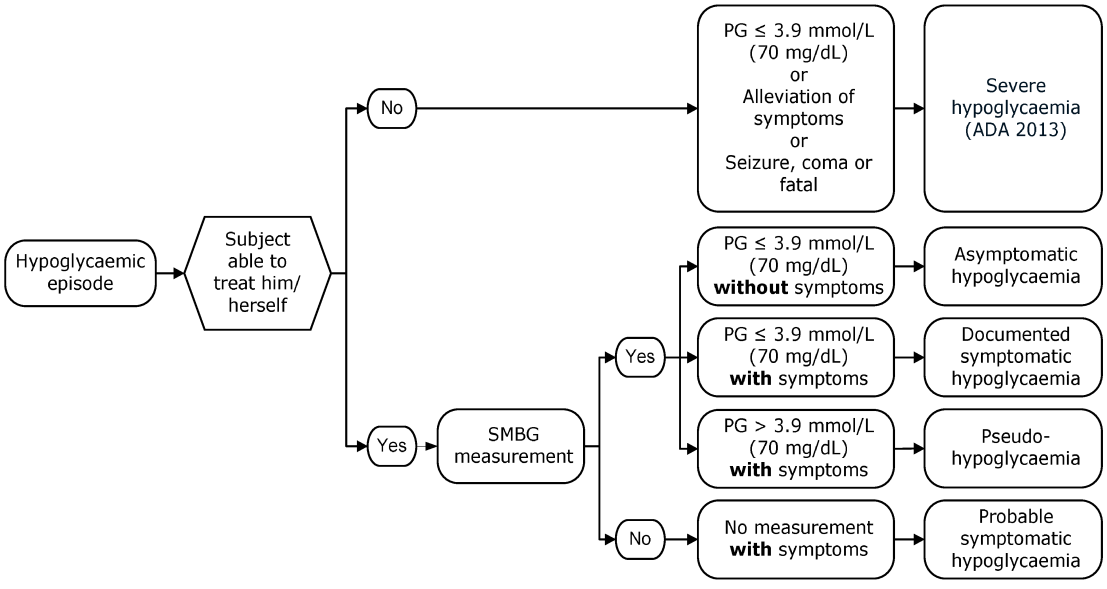


Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–2 Novo Nordisk classification of hypoglycaemia

ADA classification[36] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values

Figure 17–3 ADA classification of hypoglycaemia

Data on treatment emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one episode, the percentage of subjects with at least one episode (%), the total number of episodes and the episode rate per 100 years of exposure. Summaries of treatment emergent hypoglycaemic episodes will be presented as an overview including all episodes and episodes by severity.

Number of severe or BG confirmed symptomatic hypoglycaemic episodes

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period covered by the subject's on-treatment observation period as offset. The model will include factors for treatment and region as fixed factors and baseline HbA_{1c} as covariate.

Severe or BG confirmed symptomatic hypoglycaemic episodes (yes/no)

The binary endpoint indicating whether a subject has at least one treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using a logistic regression model with treatment and region as fixed factors and baseline HbA_{1c} as covariate.

17.5 Health economics and/or patient reported outcomes

The PRO questionnaires, SF-36v2™ and DTSQs, derived endpoints for overall scores and domains will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as covariate.

18 Ethics

18.1 Benefit-risk assessment of the trial

18.1.1 Risks and precautions

18.1.1.1 Semaglutide

The nonclinical safety programme of semaglutide has not revealed any identified safety issues for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity. See section 3.1.4.

The sections below describe identified and potential risks associated with semaglutide treatment, based on findings with other GLP-1 RAs and observations in nonclinical and clinical trials with semaglutide administered s.c. once-weekly. For each of these risks, mitigating actions have been implemented to minimise the risks for subjects enrolled in this trial.

Thyroid C-cell tumour

The human relevance of the proliferative C-cell changes found in rodents is unknown, but data suggest that rodents are more sensitive to the mode of action of GLP-1 RAs for induction of C-cell tumours with GLP-1 RAs. Recently published data have shown that the GLP-1 receptor is not expressed in the normal human thyroid. Accordingly, the risk of GLP-1 receptor mediated C-cell changes in humans is considered to be low.[25] However, as a precaution, subjects with a family or personal history of Multiple Endocrine Neoplasia Type 2, familial Medullary Thyroid Carcinoma, personal history of non-familial Medullary Thyroid Carcinoma, and subjects with a screening calcitonin ≥50 ng/L will be excluded from the trial. During the trial, calcitonin will be measured on a regular basis and guidance for investigators of further evaluation and action on elevated calcitonin concentrations will be carried out. This will ensure appropriate and consistent handling of elevated calcitonin levels across trials.

Teratogenicity (nonclinical embryo-foetal toxicity)

Semaglutide has been concluded teratogenic in rats. This effect is regarded to be caused by impairment of nutrient supply to the embryo across the inverted yolk sac with placental function. As the yolk sac does not play such a role for nutrition of the embryo in humans, this effect is not considered relevant for humans. However, as a precaution, subjects fulfilling the following exclusion criteria will be excluded: female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using an adequate contraceptive methods throughout the trial including the 5 week follow-up period (adequate contraceptive measures as required by local regulation or practice).

Gastrointestinal adverse events

Consistent with findings from other GLP-1 RAs, the most frequently reported AEs in the clinical trials with semaglutide thus far have been gastrointestinal disorders (nausea, vomiting, diarrhoea, dyspepsia and constipation). In the completed trial (NN9535-3819) a slower dose-escalation regimen was used compared to previous trials, and this substantially improved the gastrointestinal tolerability profile. Therefore, a 4-week dose escalation regimen has been developed and is used in the ongoing clinical phase 3 programme for semaglutide administered s.c. once-weekly.

Diabetic retinopathy complications

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive antidiabetic treatment.[45-47] Risk factors for these complications include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large improvements in blood glucose may be an additional aggravating factor. Several studies have, however, documented long-term beneficial effects of intensive glycaemic treatment in reducing retinopathy progression[48, 49] even in intensively treated patients who experienced early worsening.[46] In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of complications related to diabetic retinopathy in subjects treated with semaglutide compared with placebo.[50] As a precaution in this trial, all subjects are required to have fundus photography or fundoscopy performed before enrolment into the trial; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded. As part of good diabetes management the investigator is encouraged to ensure adequate monitoring and treatment of diabetic retinopathy in subjects enrolled into the trial.[51]

Allergic reactions and injection site reactions

As is the case with all protein based pharmaceuticals, subjects treated with semaglutide risk developing immunogenic and allergic reactions. These may include localised injection site reactions or generalised reactions including urticaria, rash or pruritus. Severe allergic reactions such as anaphylactic reactions could potentially also pose a risk for subjects treated with semaglutide.

Hypoglycaemia

Based on current knowledge about the GLP-1 RA drug class, there is a risk of hypoglycaemic episodes. Hypoglycaemic episodes have mainly been observed when a GLP-1 RA is combined with sulfonylurea or insulin. The risk for development of hypoglycaemia specifically with semaglutide in combination with sulfonylurea and insulin is unknown due to limited data.

Altered renal function

- Untoward effects of volume depletion, resulting from nausea, vomiting and dehydration, such as acute renal failure have been observed in subjects treated with GLP-1 RAs including

semaglutide. Impaired renal function may increase the risk of metformin associated lactic acidosis when GLP-1 RAs are co-administered with metformin. As a precaution serum creatinine is measured regularly. In subjects treated with metformin who experience prolonged or severe nausea and vomiting, the investigator should monitor serum creatinine, and if clinically indicated, withhold metformin until resolution of the renal dysfunction.

Acute pancreatitis

- Acute pancreatitis, including reports of severe necrotising and haemorrhagic forms, has been associated with GLP-1 RAs. However, data from observational studies suggest an increased frequency of pancreatitis among diabetics and a relationship between pancreatitis and GLP-1 RAs can neither be established nor excluded.[52, 53] As a precaution subjects with a history of acute or chronic pancreatitis will be excluded from the trial. Subjects will be monitored for elevated levels of amylase and lipase and be informed of the characteristic symptoms of acute pancreatitis.

Pancreatic cancer

- There is currently no support from non-clinical or clinical trials or post-marketing data that GLP-1-based therapies increase the risk of pancreatic cancer. However, as the long-term effects of stimulation of β-cells and suppression of α-cells are largely unknown, pancreatic cancer is considered a potential risk by the European Medicine Agency (EMA).

18.1.1.2 Dulaglutide

Being a GLP-1 RA dulaglutide shares many of the same potential risks for the subject as semaglutide. Please consult the EU SmPC,[28] US prescribing information[29] and the local prescribing information (non-US and non-EU countries) for dulaglutide (Trulicity®) for the following information on warnings and precautions/risks gathered under clinical trials and from post marketing data: thyroid C-cell tumours, acute pancreatitis, hypoglycaemia, hypersensitivity, severe gastrointestinal disease.

18.1.1.3 General precautions

All subjects will be included after a thorough evaluation in regards to in- and exclusion criteria defined in order to ensure that subjects are eligible for trial treatment. There are strict glycaemic rescue criteria in place to ensure acceptable glycaemic control at all times during the trial. It is the responsibility of the investigator to ensure the best possible care according to the principles outlined in Diabetes Care 2014 Standards of Medical Care in Diabetes.[54]

18.1.2 Benefits

In this trial subjects will be randomised to one of four treatment arms involving a treatment regimen anticipated to be more efficacious than the treatment they receive at the time of entry into the trial.

Semaglutide has in a phase 2 trial (NN9535-1821) proven to have a clinical meaningful and dose-dependent effect on HbA_{1c}, FPG and body weight. Doses ≥0.8 mg weekly brought more subjects to target with regards to HbA_{1c} and FPG, and provided a greater weight loss than liraglutide 1.8 mg daily. Dulaglutide has shown non-inferiority on glycaemic control versus liraglutide and the drug has already been approved for the use in subjects with T2D.

It is expected that all subjects will benefit from participation through close contact with the trial site, with close follow-up of their diabetes, and a careful medical examination; all of which will most likely result in an intensified management of their diabetes.

All subjects in this trial will receive trial drug and auxiliary supplies free of charge.

18.1.3 Risk and benefit conclusion

It is concluded that the potential benefits from participating in the trial outweigh the potential risks. The safety profile of semaglutide generated from the clinical and nonclinical development programme has not revealed any safety issues that would prohibit administration of once-weekly doses in accordance with the planned clinical trial. Dulaglutide is already a marketed drug approved for the use in subjects with T2D. It is concluded that the risk to the subjects in this trial is low and acceptable in view of the benefits a long-acting GLP-1 RA would provide to subjects with T2D.

18.2 Informed consent

In seeking and documenting informed consent, the investigator must comply with applicable regulatory requirement(s) and adhere to ICH GCP[55] and the requirements in the Declaration of Helsinki.[2]

Before any trial-related activity, the investigator must give the subject verbal and written information about the trial and the procedures involved in a form that the subject can read and understand.

The subjects must be fully informed of their rights and responsibilities while participating in the trial as well as possible disadvantages of being treated with the trial products.

The investigator must ensure the subject ample time to come to a decision whether or not to participate in the trial.

A voluntary, signed and personally dated informed consent must be obtained from the subject before any trial-related activity.

The responsibility for seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local

requirements. The written informed consent must be signed and personally dated by the person who seeks the informed consent before any trial-related activity.

If information becomes available that may be relevant to the subject's willingness to continue participating in the trial, the investigator must inform the subject in a timely manner, and a revised written subject information must be provided and a new informed consent must be obtained.

18.3 Data handling

If the subject is withdrawn from the trial or lost to follow up, then the subject's data will be handled as follows:

- Data already collected and data collected at the end-of-trial visit will be retained by Novo Nordisk, entered into the database and used for the trial report.
- Safety events will be reported to Novo Nordisk and regulatory authorities according to local/national requirements.

If data is used, it will always be in accordance with local regulations and IRBs/IECs.

18.4 Information to subject during trial

The site will be offered a communication package for the subject during the conduct of the trial. The package content is issued by Novo Nordisk. The communication package will contain the letters intended for distribution to the subjects. The letters will be translated and adjusted to local requirements and distributed to the subject by discretion of the investigator. The subject may receive a "welcome to the trial letter" and a "thank you for your participation letter" after completion of the trial. Further the subject may receive letters during the trial.

All written information to subjects must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

18.5 Premature termination of the trial and/or trial site

Novo Nordisk, the IRBs/IECs or a regulatory authority may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IRBs/IECs in case it has an impact on the planned follow-up of subjects who have

participated in the trial. If it has an impact, the actions needed to inform and protect the subjects should be described.

19 Protocol compliance

Deviations from the protocol should be avoided.

If deviations do occur, the investigator must inform the monitor and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the clinical database.

Documentation on protocol deviations must be kept in the investigator's trial master file and sponsor trial master file.

20 Audits and inspections

Any aspect of the clinical trial may be subject to audits conducted by Novo Nordisk or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as Novo Nordisk staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are relevant to the evaluation of the trial.

21 Critical documents

Before a trial site is allowed to start screening subjects, the following documents must be available to Novo Nordisk:

- Regulatory approval and/or acknowledgement of notification as required
- Approval/favourable opinion from IRBs/IECs clearly identifying the documents reviewed as follows: protocol, any protocol amendments, subject information/informed consent form, any other written information to be provided to the subject and subject recruitment materials
- List of IRB/IEC members and/or constitution (or a general assurance number/statement of compliance)
- Curricula vitae of investigator and sub-investigator(s) (current, dated and signed - must include documented GCP training or a certificate)
- Signed receipt of IB and local label of comparator
- Signed and dated Agreement on Protocol
- Signed and dated agreement on protocol amendment, if applicable
- Contract, signed by the investigator and/or appropriate parties on behalf of the investigator's site and Novo Nordisk
- Source document agreement
- Central laboratory certification and normal ranges
- Insurance statement, if applicable
- Financial disclosure form from investigator and sub-investigator(s)

- For US trial sites: verification under disclosures per Code of Federal Regulations of Financial Conflict of Interest
- For US trial sites: FDA form 1572 must be completed and signed by the investigator at each site

FDA form 1572:

For US sites:

- Intended for US sites
- Conducted under the Investigational New Drug Application (IND)
- All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

- Intended for participating sites outside of the US
- Not conducted under the IND
- All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the trial.

By signing the protocol, each investigator agrees to comply fully with ICH GCP,[55] applicable regulatory requirements and the Declaration of Helsinki.[2]

By signing the protocol, each investigator also agrees to allow Novo Nordisk to make investigator's name and information about site name and address publically available if this is required by national or international regulations.

22 Responsibilities

The investigator is accountable for the conduct of the trial at his/her site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified trial-related duties. The investigator must ensure that there is adequate training for all staff participating in the conduct of the trial. It is the investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the subjects.

A qualified physician, who is an investigator or a sub-investigator for the trial, must be responsible for all trial-related medical decisions.

The investigator must ensure adequate supervision of the conduct of the trial at the trial site.

The investigator will follow instructions from Novo Nordisk when processing data.

The investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the investigator trial master file. The documents including the subject identification code list should be kept in a secure locked facility, so no unauthorized persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of subjects to a specific qualified physician who will be readily available to subjects during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g. if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

23 Reports and publications

The information obtained during the conduct of this trial is considered confidential, and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the trial product. All information supplied by Novo Nordisk in connection with this trial shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this trial. The information obtained during this trial may be made available to other physicians who are conducting other clinical trials with the trial product, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this trial to researchers who require access for research projects studying the same disease and/or trial product studied in this trial.

Novo Nordisk may publish on its clinical trials website a redacted clinical trial report for this trial.

One (or more) investigator(s) will be appointed by Novo Nordisk to review and sign the clinical trial report (signatory investigator(s)) on behalf of all participating investigators. The signatory investigator(s) will be appointed based upon the criteria defined by the International Committee of Medical Journal Editors for research publications.[56]

23.1 Communication of results

Novo Nordisk commits to communicating, and otherwise making available for public disclosure, results of trials regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or disclosure by other means.

The results of this trial will be subject to public disclosure on external web sites according to international and national regulations, as reflected in the Novo Nordisk Code of Conduct for Clinical Trial Disclosure.[57]

Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the clinical trial report is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire trial.

At the end of the trial, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases the trial results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. All authors will be given the relevant statistical tables, figures, and reports needed to evaluate the planned publication. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

Where required by the journal, the investigator from each trial site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

Novo Nordisk maintains the right to be informed of plans by any investigator to publish and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to Novo Nordisk before submission for comments. Comments will be given within four weeks from receipt of the planned communication.

23.1.1 Authorship

Authorship of publications should be in accordance with the Uniform Requirements of the International Committee of Medical Journal Editors[56] (sometimes referred to as the Vancouver Criteria).

Novo Nordisk will appoint investigator(s) to prepare publications in collaboration with Novo Nordisk.

23.1.2 Site-specific publication(s) by investigator(s)

For a multi-centre clinical trial, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or subjects, and therefore may not be supported by Novo Nordisk. It is a Novo Nordisk policy that such individual reports do not precede the primary manuscript and should always reference the primary manuscript of the trial.

Novo Nordisk reserves the right to prior review of such publications. Further to allow for the primary manuscript to be published as the first, Novo Nordisk asks for deferment of publication of individual site results until the primary manuscript is accepted for publication. As Novo Nordisk wants to live up to the industry publication policy, submission of a primary publication will take place no later than 18 months after trial completion.

23.2 Investigator access to data and review of results

As owner of the trial database, Novo Nordisk has the discretion to determine who will have access to the database. Individual investigators will have their own research subjects' data, and will be provided with the randomisation code after results are available.

24 Retention of clinical trial documentation

24.1 Retention of clinical trial documentation

Subject's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

The investigator must agree to archive the documentation (this includes both electronic and paper-based records) pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The investigator should not destroy any documents without prior permission from Novo Nordisk. If the investigator cannot archive the documents at the trial site, Novo Nordisk can refer the investigator to an independent archive provider that has a system in place to allow only the investigator to access the files.

The investigator must be able to access his/her trial documents without involving Novo Nordisk in any way. Site-specific CRFs and other subject data (in an electronic readable format or as paper copies or prints) will be provided to the investigator before access is revoked to the systems supplied by Novo Nordisk. These data must be retained by the trial site. If the provided data (e.g. the CD-ROM) is not readable during the entire storage period, the investigator can request a new copy. A copy of all data will be stored by Novo Nordisk.

Novo Nordisk will maintain Novo Nordisk documentation pertaining to the trial for as long as the product is on the market plus 20 years.

The files from the trial site/institution must be retained for 15 years after the completion of the trial, or longer if required by local regulations or Novo Nordisk. In any case trial files cannot be destroyed until the trial site/institution is notified by Novo Nordisk. The deletion process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

25 Institutional Review Boards/Independent Ethics Committees and regulatory authorities

IRB/IEC:

Written approval or favourable opinion must be obtained from IRB/IEC prior to commencement of the trial.

During the trial, the investigator or Novo Nordisk, as applicable, must promptly report the following to the IRB/IEC, in accordance with local requirements: updates to Investigator's Brochure, unexpected SAEs where a causal relationship cannot be ruled out, protocol amendments according to local requirements, deviations to the protocol implemented to eliminate immediate hazards to the subjects, new information that may affect adversely the safety of the subjects or the conduct of the trial (including new benefit-risk analysis in case it will have an impact on the planned follow-up of the subjects), annually written summaries of the trial status, and other documents as required by the local IRB/IEC.

The investigator must ensure submission of the clinical trial report synopsis to the IRB/IEC.

Protocol amendments must not be implemented before approval or favourable opinion according to local regulations, unless necessary to eliminate immediate hazards to the subjects.

The investigator must maintain an accurate and complete record of all submissions made to the IRB/IEC. The records must be filed in the investigator trial master file and copies must be sent to Novo Nordisk.

Regulatory Authorities:

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the clinical trial report according to national requirements.

26 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical trials in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence, or any other liability of the sites or investigators conducting the trial, or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with:

Germany: German Drug Law dated August 24, 1976, last amended by article 3 of the law dated December 17, 2014 (Federal Law Gazette I p. 2222).

France: The French Public Health Code article L 1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004. "The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research."

27 References

1. International Conference of Harmonisation. ICH Harmonised Tripartite Guideline E6(R1): Guideline for Good Clinical Practice. 10 Jun 1996.
2. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.
3. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am. 2004;88(4):787-835, ix.
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53.
5. Chuang LM, Tsai ST, Huang BY, Tai TY, Diabcare-Asia Study Group. The status of diabetes control in Asia--a cross-sectional survey of 24 317 patients with diabetes mellitus in 1998. Diabet Med. 2002;19(12):978-85.
6. Ford ES, Li C, Little RR, Mokdad AH. Trends in A1C concentrations among U.S. adults with diagnosed diabetes from 1999 to 2004. Diabetes Care. 2008;31(1):102-4.
7. Holst JJ, Vilsboll T, Deacon CF. The incretin system and its role in type 2 diabetes mellitus. Mol Cell Endocrinol. 2009;297(1-2):127-36.
8. Kieffer TJ, Habener JF. The glucagon-like peptides. Endocr Rev. 1999;20(6):876-913.
9. Hare KJ, Vilsboll T, Holst JJ, Knop FK. Inappropriate glucagon response after oral compared with isoglycemic intravenous glucose administration in patients with type 1 diabetes. Am J Physiol Endocrinol Metab. 2010;298(4):E832-7.
10. Nauck MA. Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. Am J Med. 2011;124(1 Suppl):S3-18.
11. Flint A, Kapitza C, Hindsberger C, Zdravkovic M. The once-daily human glucagon-like peptide-1 (GLP-1) analog liraglutide improves postprandial glucose levels in type 2 diabetes patients. Adv Ther. 2011;28(3):213-26.
12. Kapitza C, Flint A, Hindsberger C, Zdravkovic M. The effect of the once-daily human GLP-1 analogue liraglutide on the pharmacokinetics of paracetamol. Diabetes. 2008;57(Suppl. 1):A593-A.
13. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest. 1998;101(3):515-20.
14. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsboll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011;96(3):737-45.
15. Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. Diabetologia. 1986;29(1):46-52.
16. Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? Diabetologia. 2011;54:10-8.
17. Perley MJ, Kipnis DM. Plasma Insulin Responses to Oral and Intravenous Glucose - Studies in Normal and Diabetic Subjects. Journal of Clinical Investigation. 1967;46(12):1954-&.

18. Hojberg PV, Vilsboll T, Rabol R, Knop FK, Bache M, Krarup T, et al. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. Diabetologia. 2009;52(2):199-207.
19. Holst JJ. Enteroglucagon. Annu Rev Physiol. 1997;59:257-71.
20. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 1993;36(8):741-4.
21. Toft-Nielsen MB, Madsbad S, Holst JJ. Determinants of the effectiveness of glucagon-like peptide-1 in type 2 diabetes. J Clin Endocrinol Metab. 2001;86(8):3853-60.
22. Hansen L, Deacon CF, Orskov C, Holst JJ. Glucagon-like peptide-1-(7-36)amide is transformed to glucagon-like peptide-1-(9-36)amide by dipeptidyl peptidase IV in the capillaries supplying the L cells of the porcine intestine. Endocrinology. 1999;140(11):5356-63.
23. Larsen J, Hylleberg B, Ng K, Damsbo P. Glucagon-like peptide-1 infusion must be maintained for 24 h/day to obtain acceptable glycemia in type 2 diabetic patients who are poorly controlled on sulphonylurea treatment. Diabetes Care. 2001;24(8):1416-21.
24. ICH Harmonised Tripartite Guideline. Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2). 2009.
25. Waser B, Blank A, Karamitopoulou E, Perren A, Reubi JC. Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas. Mod Pathol. 2015;28(3):391-402.
26. Novo Nordisk A/S. Investigator's Brochure, s.c. Semaglutide (NN9535), Edition 10 or any updates hereof. 2015.
27. Dungan KM, Povedano ST, Forst T, Gonzalez JG, Atisso C, Sealls W, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet. 2014;384(9951):1349-57.
28. EU SmPC for Dulaglutide. 12/19/2014 2014.
29. Eli Lilly and Company. Trulicity® (dulaglutide), US Prescribing information (PI). Sep 2014.
30. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364-79.
31. Novo Nordisk A/S. How we disclose trial information. 2015.
32. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med. 2004;351(12):1250-1.
33. U.S. Department of Health and Human Services, Food and Drug Administration. Food and Drug Administration Amendments Act of 2007.
34. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the

laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, article 11. Official Journal of the European Communities. 01 May 2001.

35. The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. Official Journal of the European Communities. April 2001.
36. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, 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.
37. McAulay V, Deary IJ, Frier BM. Symptoms of hypoglycaemia in people with diabetes. Diabet Med. 2001;18(9):690-705.
38. European Commission. The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13, Investigational Medicinal Products (ENTR/F/2/AM/an D[2010] 3374). 03 Feb 2010.
39. Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med. 2009;28(4):586-604.
40. Rohmeyer K, Klinglmueller F. gMCP: Graph Based Multiple Test Procedures. R package version 0.8-8. 3 Oct 2014.
41. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1). 2 Jul 2010.
42. National Academy of Sciences (NAS). The Prevention and Treatment of Missing Data in Clinical Trials. Washington D.C.: The National Academies Press. 2010.
43. Little RJA, Rubin DB. Statistical analysis with missing data: New York: John Wiley & Sons. 1987.
44. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. J Clin Invest. 1987;79(3):777-81.
45. Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. Br Med J (Clin Res Ed). 1985;290(6471):811-5.
46. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol. 1998;116(7):874-86.
47. Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes Res Clin Pract. 2014;103(3):e37-9.
48. UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes

(UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53, Erratum 1999; 354: 602.

49. The Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. Diabetes Care. 2016;39(7):1089-100.
50. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016.
51. American Diabetes Association. Standards of medical care in diabetes - 2016. Diabetes Care. 2016;39 (Suppl. 1):S1-S109.
52. Wenten M, Gaebler JA, Hussein M, Pelletier EM, Smith DB, Girase P, et al. Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medication: a follow-up study. Diabet Med. 2012;29(11):1412-18.
53. Yang L, He Z, Tang X, Liu J. Type 2 diabetes mellitus and the risk of acute pancreatitis: a meta-analysis. Eur J Gastroenterol Hepatol. 2013;25(2):225-31.
54. Standards of medical care in diabetes. Diabetes Care. 2014;37(Supplement 1):S14-S80.
55. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline for Good Cinical Practice. Geneva, Switzerland. 5/1/1996 1996.
56. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 12/16/2014 2014.
57. Novo Nordisk A/S. http://www.novonordisk-trials.com/website/content/how-we-disclose-trial-information.aspx.

Protocol Amendment

no 01
to Protocol, final version 1.0
dated 14 July 2015

Trial ID: NN9535-4216

Efficacy and safety of semaglutide versus dulaglutide as add-on to metformin in subjects with type 2 diabetes

Trial phase: 3b

Applicable to Portugal

Redacted protocol
Includes redaction of personal identifiable information only.

Amendment originator:

[redacted], [redacted]

Medical Department, Portugal

Table of Contents

Page

1 Introduction including rationale for the protocol amendment

The rationale for this protocol amendment is clarification on the adequate contraceptive measure acceptable for Portugal.

According to the Clinical Trials Facilitation Group (CTFG) on the Recommendations related to contraception and pregnancy testing in clinical trials (2014) the study protocol should contain detailed information on the level of contraception and the possibility for an interaction between the IMP or the non-investigational medicinal products and hormonal contraceptives, the frequency of pregnancy testing, and the duration of the need for contraceptive measures and pregnancy testing.

In this protocol amendment:

- Any new text is written *in bold italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

6.3 Exclusion criteria (page 27)

For an eligible subject, all exclusion criteria must be answered "no".

3. Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using an adequate contraceptive method (adequate contraceptive measures as required by local regulation or practice). *Germany: Only highly effective methods of birth control are accepted (i.e. one that results in less than 1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or sexual abstinence or vasectomised partner. Ireland: Adequate contraceptive measures are defined as established use of combined oral contraceptives, injected or implanted hormonal methods of contraception, sterilisation, intrauterine device or intrauterine system or consistent use of barrier methods together with the use of spermicide and sexual abstinence. United Kingdom: Adequate contraceptive measures are defined as established use of oral, intravaginal, transdermal combined estrogen and progestogen hormonal methods of contraception; oral, injected or implanted progestogen only hormonal methods of contraception; placement of an intrauterine device or intrauterine hormone releasing system, bilateral tubal occlusion, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), female sterilisation, vasectomised partner (where partner is sole partner of subject), or true abstinence (when in line with preferred and usual lifestyle).* ***Portugal: Only highly effective methods of birth control (i.e. one that results in less than 1% per year failure rate when used consistently) are accepted, such as sexual abstinence (when in line with the preferred and usual lifestyle), combined (estrogen and progestogen containing) hormonal contraception associated with***

inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion or vasectomised partner.

Protocol Amendment

no. 02 Global
to Protocol, final version 1.0
dated 14 July 2015

Trial ID: NN9535-4216

Efficacy and safety of semaglutide versus dulaglutide as add-on to metformin in subjects with type 2 diabetes

Trial phase: 3b

Applicable to all countries

Redacted protocol
Includes redaction of personal identifiable information only.

Amendment originator:

[redacted], [redacted]

Trial Operations, Semaglutide Diabetes & Diabetes Outcomes

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1 Introduction including rationale for the protocol amendment

The main objective of this global protocol amendment is to align the Risks and Precautions section of the protocol (section 18.1.1) with edition 11, amendment 1, version 2.0 of the Investigator's Brochure for subcutaneous semaglutide in order to include new information on diabetes retinopathy complications, as observed in the SUSTAIN 6 cardiovascular outcomes trial (NN9535-3744).

In addition, updates for general clarification have been done (see section 2.2–2.7) and new references have been included (see section 2.8). Attachment I has been updated with new key staff and vendor information (see section 3.1). The rationale for each of these changes is given just after the description of each change.

In this protocol amendment:

- Any new text is written *in italics.*
- Any text deleted from the protocol is written using ~~strike through~~.

2 Changes

2.1 Section 18.1.1.1 Semaglutide

Diabetic retinopathy complications

A transient worsening of diabetic retinopathy is a recognised complication in selected patients with diabetes after initiation of intensive antidiabetic treatment.[45-47] Risk factors for these complications include long-standing poor glycaemic control and presence of proliferative retinopathy, and initial large improvements in blood glucose may be an additional aggravating factor. Several studies have, however, documented long-term beneficial effects of intensive glycaemic treatment in reducing retinopathy progression[48, 49] even in intensively treated patients who experienced early worsening.[46] In a cardiovascular outcomes trial with s.c. semaglutide, results indicate an increased risk of complications related to diabetic retinopathy in subjects treated with semaglutide compared with placebo.[50] As a precaution in this trial, all subjects are required to have fundus photography or fundoscopy performed before enrolment into the trial; moreover, subjects with proliferative retinopathy or maculopathy requiring acute treatment will be excluded. As part of good diabetes management the investigator is encouraged to ensure adequate monitoring and treatment of diabetic retinopathy in subjects enrolled into the trial.[51]

[New text to be placed after "Gastrointestinal adverse events". Please see section 2.8 of this protocol amendment for the references].

Rationale: See section 1 of the amendment.

2.2 Section 8.1.6 Premature discontinuation of trial product

Subjects discontinuing trial product prematurely should continue with the scheduled site contacts after visit 9A *and phone contact 10A* ~~has~~*have* been conducted.

Rationale: A correction to clarify that trial subjects should resume the scheduled site contacts only after visit 9A **and** phone contact 10A have been conducted. This is in alignment with the text in the Subject Information/Informed Consent form and the previous SUSTAIN trials.

2.3 Section 8.4.7 Calcitonin

In case any calcitonin value at any time of the trial is ~~>10 ng/L~~ *≥10 ng/L*, the algorithm in appendix B should be followed.

Rationale: Correction of a typo whereby the value specified for calcitonin does not match the value specified in appendix B.

2.4 Section 8.6.1 Subject diary

Subjects who prematurely discontinue from trial product are not required to use diaries for subsequent scheduled visits after the follow-up premature discontinuation visit (P10A).

[Text to be placed after the paragraph beginning "The diaries should be handed out/collected as indicated in the flow chart"].

Rationale: To clarify that subjects who discontinue trial product but remain in the trial do not need to use subject diaries for scheduled visits after the follow-up premature discontinuation visit (P10A).

2.5 Section 8.1.5 Fasting visits

~~The subjects should attend site visits in a fasting state (see section 2 for details). Fasting is defined as having consumed only water within the last 6 hours prior to the visit. Glucose lowering agents and trial product cannot be taken until after blood sampling has been performed but other prescribed medication should be taken according to prescription.~~

~~If the subject does not attend the visit in a fasting state, the subject should be asked to attend a rescheduled visit within the visit window to have the fasting assessments performed.~~

The subjects should attend site visits in a fasting state (see section 2 for details). Fasting is defined as having consumed only water within the last 6 hours prior to the visit.

If the subject does not attend the visit in a fasting state, the subject should be asked to attend a rescheduled visit within the visit window to have the fasting assessments performed.

Glucose lowering agents and trial product should not be taken until after blood sampling has been performed but other prescribed medication should be taken according to prescription.

Rationale: To clarify that subjects who take trial product on the day of the site visit, but prior to lab sampling, are considered as fasting. **Note that no new text has been added or deleted as part of this change**; the order of the text has instead been updated to make the section more clear.

2.6 Table 12-1 Adverse events with additional data collection

Event	**Event adjudication**	**Special eCRF form**
Fatal event	Yes	No
Acute coronary syndrome	Yes	Yes
Cerebrovascular event	Yes	Yes
Heart failure requiring hospitalisation	Yes	Yes
Pancreatitis	Yes	Yes
Thyroid disease (including thyroid neoplasm)	Yes~~,~~ (only if thyroid neoplasm or resulting in thyroidectomy)	Yes
~~Malignant n~~Neoplasm (excluding thyroid neoplasm)	Yes *(only if malignant)*	Yes
Hypersensitivity reactions	No	Yes

Rationale: To clarify that all neoplasms should be considered adverse events requiring additional data collection, but that only malignant neoplasms require adjudication. This update will align the information in Table 12-1, section 8.7 (Adverse events with additional data collection), and Table 12-2 (Adverse events for adjudication).

2.7 Section 8.7 Adverse events with additional data collection

Selected events (cardiovascular events, pancreatitis, thyroid disease and *malignant* neoplasm) will be adjudicated and for further details on the definitions, please refer to Table 12–2.

Rationale: Please refer to the rationale for section 2.6.

2.8 Section 27 References

45. *Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. Br Med J (Clin Res Ed). 1985;290(6471):811-5.*
46. *The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol. 1998;116(7):874-86.*
47. *Varadhan L, Humphreys T, Walker AB, Varughese GI. The impact of improved glycaemic control with GLP-1 receptor agonist therapy on diabetic retinopathy. Diabetes Res Clin Pract. 2014;103(3):e37-9.*
48. *UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352(9131):837-53, Erratum 1999; 354: 602.*
49. *The Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group. Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study. Diabetes Care. 2016;39(7):1089-100.*
50. *Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016.*
51. *American Diabetes Association. Standards of medical care in diabetes - 2016. Diabetes Care. 2016;39 (Suppl. 1):S1-S109.*

Rationale: To add the seven references cited in the new text on diabetic retinopathy complications in protocol section 18.1.1.1 (see section 2.1 of this protocol amendment). Inclusion of these references will change the numbering of the subsequent references in the protocol.

3 Changes in protocol attachments

3.1 Attachment I – Global list of key staff and relevant departments and suppliers of clinical relevance

International Trial Manager(s):	Name:	[redacted]
	Title:	[redacted]
	Tel:	[redacted]
	E-mail:	[redacted]
Customer Complaint Center, (Contact for technical complaints):	Name:	Novo Nordisk A/S Att: Customer Complaint Center
	Address:	Krogshoejvej ~~44~~ *55*
Central Laboratory*:*	Name:	[redacted]
	Tel:	[redacted]
	~~Fax:~~	[redacted]
	E-mail:	[redacted]
Special Laboratory:	Name:	Novo Nordisk Maaloev ~~Cell and Antibody Analysis, Diabetes & GH~~ *Immunogenicity Assessment*

Rationale: To capture updated key staff and vendor information.

Statistical Analysis Plan

Trial ID: NN9535-4216

SUSTAIN 7

Efficacy and safety of semaglutide versus dulaglutide as add-on to metformin in subjects with type 2 diabetes

Trial phase: 3b

Author:
[redacted], Trial Statistician
Biostatistics

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List of abbreviations

AACE	American Association of Clinical Endocrinologists
ADA	American Diabetes Association
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BG	Blood glucose
BMI	Body mass index
BW	Body weight
CHF	Congestive Heart Failure
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	Confidence interval
CV	Cardiovascular
CV	Coefficient of variation
CTR	Clinical trial report
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EAC	Event adjudication committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EoT	End of text
EOT	End of treatment
FAS	Full analysis set
FDA	US Food and Drug Administration
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate
HbA_{1c}	Glycosylated haemoglobin
HDL	High density lipoprotein
HOMA-B	Homeostasis model assessment
HR	Hazard ratio
ITT	Intention-to-treat
IV/WRS	Interactive voice/web response system
LDL	Low density lipoprotein
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed model for repeated measures
PP	Per protocol
PRO	Patient reported outcome

PYO	Patient years of observation time
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
s.c.	subcutaneous
SD	Standard deviation
SE	Standard error
SEM	Standard error of mean
SMPG	Self-measured plasma glucose
SPS	Statistical Programming Specification
T2D	type 2 diabetes
TD	Treatment difference
ULOQ	Upper limit of quantification

1 Introduction

1.1 Trial information

This trial is 40-week randomised, open-label, active-controlled, parallel group, multicentre, multinational, four-armed trial to evaluate efficacy and safety of semaglutide versus dulaglutide as add-on to metformin in subjects with type 2 diabetes.

Primary objective
To compare the effect of once-weekly dosing of two dose levels of subcutaneous semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of two dose levels of subcutaneous dulaglutide (0.75 mg and 1.5 mg) on glycaemic control in subjects with type 2 diabetes on a background treatment with metformin.

Key secondary objective
To compare the effect of once-weekly dosing of two dose levels of subcutaneous semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of two dose levels of subcutaneous dulaglutide (0.75 mg and 1.5 mg) in subjects with type 2 diabetes on a background treatment with metformin with regards to body weight control, blood pressure, patient reported outcomes, and safety and tolerability.

Trial design
Subjects with type 2 diabetes inadequately controlled with metformin alone will after approximately 2 weeks screening period be randomised in a 1:1:1:1 manner to receive either a dose of 0.5 mg or 1.0 mg of semaglutide once-weekly or 0.75 mg or 1.5 mg of dulaglutide once-weekly. After the treatment period of approximately 40 weeks in total, all subjects enter a follow-up period of 5 weeks ended by a follow-up phone contact. Total trial duration for the individual subjects will be approximately 47 weeks. A planned total number of 1196 subjects will be randomised. For further details, see protocol for trial NN9535-4216.

1.2 Scope of the statistical analysis plan

This statistical analysis plan (SAP) is based on the protocol for trial NN9535-4216 “Efficacy and safety of semaglutide versus dulaglutide as add-on to metformin in subjects with type 2 diabetes”, version 2.0 (4 November 2016), and includes more detailed procedures for executing the statistical analyses of the primary and secondary endpoints. Additional analyses have been added in this SAP as compared to the protocol. All changes to the statistical analyses planned in the protocol and added secondary analyses are documented in Section 3 of this SAP.

Novo Nordisk will be responsible for the statistical analyses and reporting. Data from all sites will be analysed and reported together.

2 Statistical considerations

2.1 General considerations

No interim analyses or other analyses of unmasked or between group data will be performed before the database is locked. If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analyses. The SAP will be finalised before database lock.

Data from all trial sites will be analysed and reported together. If an assessment has been made both at screening and randomisation, and if not otherwise specified, the value from the randomisation visit will be used as the baseline value. If an assessment is missing at randomisation, but available at screening, then the screening value will be used as the baseline value.

Laboratory values below the lower limit of quantification (LLOQ) will be set to ½LLOQ.

Results from a statistical analysis will be presented by the estimated treatment contrasts at week 40 with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference if not otherwise specified.

The two principal comparisons presented from a statistical analysis are

- s.c. semaglutide 0.5 mg versus dulaglutide 0.75 mg
- s.c. semaglutide 1.0 mg versus dulaglutide 1.5 mg

2.2 Primary estimand

The primary objective of the trial is to compare the effect of once-weekly dosing of two dose levels of s.c. semaglutide (0.5 mg and 1.0 mg) versus once-weekly dosing of each of the two dose levels of s.c. dulaglutide (0.75 mg and 1.5 mg) on glycaemic control in subjects with T2D on a background treatment with metformin.

The primary estimand will be:

- de-jure treatment difference at week 40 for all randomised subjects if all subjects adhered to treatment and did not initiate antidiabetic rescue medication

This estimand assesses the glycaemic benefit a future subject is expected to achieve if he/she initiates and continue treatment with s.c. semaglutide as compared to dulaglutide. It is considered a clinically relevant estimand as it provides information to treating clinicians about the expected glycaemic efficacy of s.c. semaglutide for purposes of treating individual subjects with T2D.

2.3 Missing data considerations

Since both semaglutide and dulaglutide are GLP-1 RA, it is reasonable to assume that missing data in both arms will be similar in timing, extent and reason. Based on the phase 2 semaglutide dose finding trial (NN9535-1821) and the slower dose escalation implemented in this trial, the rate of discontinuing treatment prematurely or initiating rescue medication on top of trial product is expected to be maximum 25% and similar across treatment arms after 40 weeks of treatment.

Since efficacy for both semaglutide and dulaglutide have been shown, missing data due to ineffective therapy is not anticipated to be a notable issue. However, some missing data due to AEs is expected in both treatment arms because of gastrointestinal related AEs leading to premature treatment discontinuation primarily during initiation and dose escalation.

Descriptive summaries and graphical representation of extent, reason(s) for and pattern of missing data will be presented by treatment arm.

2.4 Sample size calculation

The primary endpoint is change from baseline in HbA_{1c} after 40 weeks of treatment. For HbA_{1c}, both non-inferiority and subsequently superiority are planned to be tested at each dose level (semaglutide 0.5 mg versus dulaglutide 0.75 mg and semaglutide 1.0 mg versus dulaglutide 1.5 mg). The confirmatory secondary endpoint is change from baseline in body weight after 40 weeks of treatment. For body weight, superiority is planned to be tested at each dose level.

The sample size calculation is based on jointly meeting four out of the six pre-specified confirmatory hypotheses shown in Figure 1. The closed testing procedure described in Bretz et al[1] is used to control the overall type-1 error at a two-sided 5% level. The four hypotheses are:

- HbA_{1c} non-inferiority of semaglutide 0.5 mg versus dulaglutide 0.75 mg (margin of 0.4%)
- Body weight superiority of semaglutide 0.5 mg versus dulaglutide 0.75 mg
- HbA_{1c} non-inferiority of semaglutide 1.0 mg versus dulaglutide 1.5 mg (margin of 0.4%)
- Body weight superiority of semaglutide 1.0 mg versus dulaglutide 1.5 mg

The sample size is calculated using the calcPower function in the R package, gMCP[2] using 10000 simulations. All of the six pre-specified confirmatory hypotheses are assumed to be independent. Since positive correlations are expected, the assumption of independence is viewed as conservative.

Furthermore, the sample size calculation is based on the following assumptions:

Based on the phase 2 s.c. semaglutide dose-finding trial (NN9535-1821), the standard deviation for HbA_{1c} is assumed to be 1.1% and the standard deviation for body weight is assumed to be 4 kg.

The assumed treatment difference in HbA_{1c} of semaglutide relative to dulaglutide at week 40 within both dose levels is zero. The assumed treatment difference in body weight of semaglutide relative to dulaglutide at week 40 within both dose levels is 1.5 kg. A 50% smaller effect on body weight is assumed in the 25% of subjects expected to discontinue treatment prematurely or initiate rescue medication on top of trial product. This leads to an adjusted treatment effect of 1.35 kg for body weight, which is the value used in the sample size calculation. Based on oral semaglutide phase 2 results (NN9924-3790), the 50% efficacy retention is viewed as conservative in light of the primary analysis but less so for the in-trial sensitivity analyses that uses all data collected during the trial.

With the above assumptions, allocating 299 subjects to each of the semaglutide and dulaglutide arms yields 90% power to confirm HbA_{1c} non-inferiority and body weight superiority between semaglutide and dulaglutide at both dose levels.

Calculated powers for selected individual hypotheses are presented in Table 1. In total 4×299 = 1196 subjects are planned to be randomised.

Table 1 Calculated powers for individual hypotheses

Statistical test	HbA_{1c} non-inferiority (margin=0.4%)		Body weight superiority		HbA_{1c} superiority	
Treatment dose level	High	Low	High	Low	High	Low
Power (%)	99	99	95	95	1.2	1.2

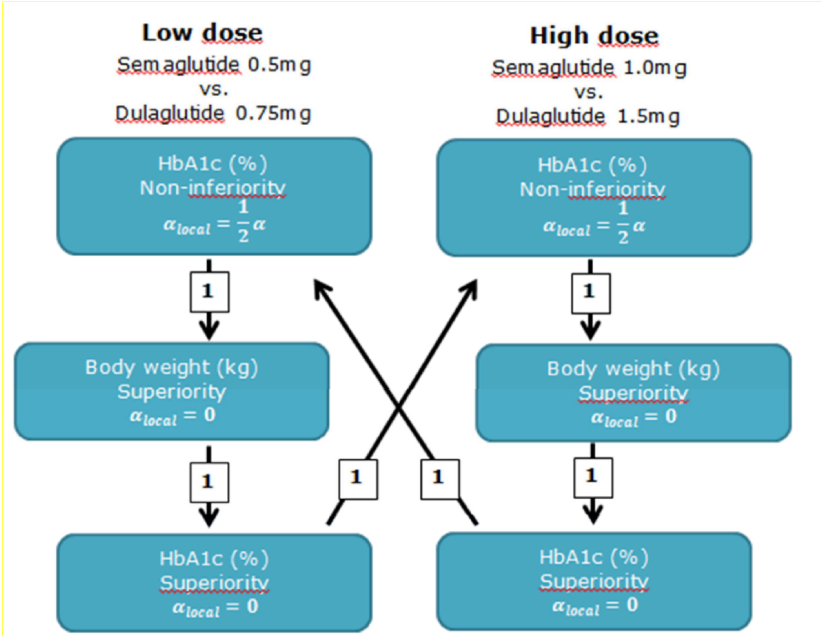

Figure 1 Graphical illustration of the closed testing procedure

The Type-I error for the six pre-specified confirmatory hypotheses will be controlled in the strong sense using the closed testing procedure in Figure 1. The initial allocation of the overall significance level of α=0.05 (two-sided) is split equally between non-inferiority at the two dose levels. The local significance level (αlocal) will be reallocated if a hypothesis is confirmed according to the weight given by directed edge between nodes (the hypotheses).

2.5 Definition of analysis sets

The following analysis sets will be defined:

Full analysis set (FAS): includes all randomised subjects exposed to at least one dose of trial product. Subjects in the FAS will contribute to the evaluation "as randomised".

Safety analysis set (SAS): includes all randomised subjects exposed to at least one dose of trial product. Subjects in the SAS will contribute to the evaluation "as treated".

Per protocol (PP) analysis set: includes all subjects in the FAS who fulfil the following criteria:

- Have not violated any inclusion criteria
- Have not fulfilled any exclusion criteria
- Have a non-missing HbA_{1c} measurement at screening and/or randomisation

- Is on trial product at week 28 and have at least one non-missing HbA_{1c} measurement at or after week 28

Subjects in the PP analysis set will contribute to the analysis "as treated".

Before data are locked for statistical analysis, a review of all data will take place. Any decision to exclude either a subject or single observations from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the FAS. The subjects or observations to be excluded, and the reasons for their exclusion will be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report.

2.6 Data selections and observations periods

Unless subjects withdraw their informed consent, data collection will continue for the full duration of the trial, which is until the follow-up phone contact (P10).

The data to be used in all analyses will be selected in two steps.

Step 1: The subjects and treatment principle (as treated or as randomised) to be used in the analysis will be selected based on the specified *analysis set*.

Step 2: Data points for subjects used in the analysis set will be selected according to whether or not the data points belongs to the specified *observation period* (In-trial, on-treatment or on-treatment without rescue as defined below). Information collected with onset date outside the observation period will be treated as missing and therefore excluded from the corresponding analysis. For adjudicated events, onset date will be the EAC adjudicated onset date.

- *In-trial*: The in-trial observation period includes observations recorded at or after randomisation (as registered in IWRS) and not after the last subject-investigator contact, which is scheduled to take place 5 weeks after planned last dose of trial product at a follow-up phone contact (P10). For subjects who withdraw their informed consent, the in-trial observation period ends at their date of withdrawal. In the case a subject dies during the trial, the date of death will be the end-date of the in-trial observation period. If a subject is lost to follow-up, the end of his/her in-trial period is defined as the date of the last subject-investigator contact (site or phone visit). Analysis based on this observation period includes data regardless of treatment exposure and/or usage of non-investigational antidiabetic medications. Since non-investigational antidiabetic medications can mask or exaggerate both the efficacy and safety effects, this observation period will be in line with the primary estimand and is considered supportive for both efficacy and safety evaluations.

- *On-treatment*: This observation period represents the time period where subjects are considered treated with trial product. The observation period is a subset of the in-trial observation period and two slightly different data handling rules will be needed to cover all assessments appropriately. For adjudicated events, ECGs and AEs including hypoglycaemic episodes, this observation period will represent information collected while subjects are considered exposed to trial product. This corresponds to information collected up until the follow-up phone contact, which is scheduled to take place 5 weeks after premature treatment discontinuation to reflect five half-lives of s.c. semaglutide including a visit window of +7 days. For the remaining safety and efficacy assessments that are collected up until and not after the end of treatment visit, the follow-up period will not be included in the on-treatment observation period. In line with the primary estimand, the on-treatment observation period will be the primary observation period used in safety evaluations.

- *On-treatment without rescue*: This observation period is a subset of the on-treatment observation period, where subjects do not receive any non-investigational antidiabetic medication (rescue medication). Specifically it includes observations recorded at or after date of first dose of trial product and not after the first occurrence of the following:
    - The last dose of trial product plus the dosing interval
    - Initiation of rescue medication

For subjects who have no post-baseline scheduled assessments available in the on-treatment without rescue period, the baseline value will be carried forward to the first scheduled visit for the associated endpoint to ensure that all randomised subjects will contribute to the statistical analysis. In line with the primary estimand, the on-treatment without rescue observation period will be the primary observation period used in efficacy evaluations.

2.7 Primary endpoint

The primary analysis used to estimate the primary estimand will be based on FAS using data from the on-treatment without rescue observation period in a Mixed Model for Repeated Measures (MMRM). A restricted maximum likelihood (REML) will be used. The model will include all post baseline HbA_{1c} measurements collected at scheduled visits up to and including week 40 data as dependent variables. The independent effects included in the model will be treatment and country as fixed effects and baseline response as covariate, all nested within visit. An unstructured covariance matrix will be employed for measurements within the same subject, assuming that measurements across subjects are independent. From this model, the two by dose level estimated treatment differences between s.c. semaglutide versus dulaglutide at week 40 will be presented together with associated two-sided 95% confidence intervals and unadjusted two sided p-values for testing non-inferiority and superiority.

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. This analysis assumes that the missing data mechanism is missing at random (MAR). Thus,

for a subject who has missing data, MAR assumes a value for the endpoint based on observed data of subjects whose baseline explanatory variables and response up to withdrawal are similar to that of the discontinued subject. Since there is no historical evidence suggesting that subjects discontinuing semaglutide prematurely have better outcome on average than those who remain on treatment, the primary analysis is not expected to bias the estimated HbA_{1c} treatment effect for the primary estimand in favour of semaglutide to any important degree. This is based on the s.c. semaglutide phase 2 (NN9535-1821) results and further supported by data from liraglutide clinical trials.

For an overview of statistical analyses to be performed for the primary endpoint HbA_{1c}, see Table 2.

Table 2 Summary of statistical analyses of primary endpoint (HbA_{1c})

Population	Period	Statistical model	Imputation[1)]	Hypothesis to be tested
Primary analyses				
FAS	On-treatment without rescue medication	MMRM[2)]	Baseline values will be carried forward to week 4 for subjects with all post-baseline values missing.	Non-inferiority
FAS	On-treatment without rescue medication	MMRM[2)]	Baseline values will be carried forward to week 4 for subjects with all post-baseline values missing.	Superiority
Sensitivity analyses				
PP	On-treatment without rescue medication	MMRM	Baseline values will be carried forward to week 4 for subjects with all post-baseline values missing.	Non-inferiority
Complete cases	On-treatment without rescue medication	ANCOVA[4)]	Not applicable	Non-inferiority

FAS	On-treatment without rescue medication	ANCOVA[4)]	Last observation carried forward for subjects with missing value at week 40	Superiority
FAS	On-treatment without rescue medication	Tipping point analysis using an ANCOVA model	Multiple imputation	Non-inferiority
FAS	On-treatment without rescue medication	Tipping point analysis using an ANCOVA model	Multiple imputation	Superiority
FAS	In-trial	Retrieved dropout analysis, using an ANCOVA model[3)]	Multiple imputation	Superiority

[1)] If a subject is missing baseline assessment, then the screening assessment will be used as the baseline assessment. If no measurement(s) have been obtained, at or prior to randomisation, the baseline value will be left missing.
[2)] MMRM model will be used to estimate the efficacy (de-jure) estimand
[3)] Retrieved dropout analysis, using an ANCOVA model, will be used to estimate the effectiveness (de-facto) estimand
[4)] Baseline and week 40 measurements will be used in the analysis

2.8 Hypotheses tested for the primary endpoint

For HbA_{1c}, the following two confirmatory hypotheses are planned to be tested at each dose level comparing; (i) semaglutide 0.5 mg versus dulaglutide 0.75 mg and (ii) semaglutide 1.0 mg versus dulaglutide 1.5 mg with mean treatment difference defined as μ=(semaglutide minus dulaglutide):

- Non-inferiority using a non-inferiority margin of 0.4
  – H_0: μ>=0.4% against H_a: μ <0.4%

- Superiority
  – H_0: μ>=0.0% against H_a: μ<0.0%

Operationally, the hypotheses will be assessed using two-sided p-values.

2.9 Multiplicity and criteria for confirming hypotheses

The Type-I error for testing the six confirmatory hypotheses related to HbA_{1c} and body weight endpoints will be preserved in the strong sense at 5% (two-sided) using the weighted Bonferroni-based closed testing procedure described in Bretz et al[1] and outlined in Figure 1. First the 2 non-inferiority hypotheses at each dose level will be tested each at its initial allocated local significance

level of 0.025%. If a non-inferiority hypothesis is confirmed, the local significance level will be reallocated according to the edge going out of the confirmed hypothesis as specified in Figure 1. Each of the following hypotheses will be tested at their local significance level (α- local). This process will be repeated until no further hypothesis can be confirmed.

Non-inferiority and/or superiority will be considered confirmed if the mean treatment difference is supporting the corresponding hypothesis and the two-sided p-value is strictly below its local two-sided significance level as defined by the closed testing procedure in Figure 1. This is equivalent to using a one-sided p-value and a one-sided 2.5% overall significance level in the closed testing procedure.

2.10 Sensitivity analyses

The aim of the below pre-specified sensitivity analyses is to explore the impact of departures from the missing data assumption made in the primary analysis of HbA_{1c} and the confirmatory secondary analysis of body weight (see section 2.11.1). This is consistent with European Medicines Agency (EMA) recommendations [3] and with a report from the US National Research Council [4]. Since conservatism (i.e. avoiding bias in favour of semaglutide) depends on the context, the sensitivity analyses are targeted to whether non-inferiority or superiority is being tested.

2.10.1 Tipping point analyses

The tipping point analyses explore the validity of the conclusions in the trial, where missing data will be handled using multiple imputation assuming that missing data is missing at random (MAR).

Tipping-point analysis (pattern mixture model based) is based on the FAS using the 'on-treatment without rescue medication' observation period. In this analysis, subjects from the semaglutide group with missing observations will be given a penalty, i.e., it is assumed that subjects with missing observations who are randomised to semaglutide will receive a treatment that is less beneficial than subjects with observed values who are randomised to semaglutide. The idea is to gradually increase the penalty to evaluate at which level the conclusion of the analyses in terms of statistical significance is changed. It can be used to evaluate the robustness of statistical significance when the extent of missing data is reasonable [5].

Intermittent missing values, within the given observation period, are imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern. This imputation is done for each of the four treatment groups separately, defined by randomised treatment, and 500 datasets will be generated. These 500 datasets have a monotone missing data pattern and will be used as data foundation for imputation of remaining monotone missing values.

For each of the 500 datasets (MCMC imputed), a sequential conditional regression approach for imputing monotone missing values at planned visits will be implemented starting with the first visit

after baseline and sequentially continuing to the last planned visit at week 40. An ANCOVA model used to impute missing values at each planned visit will be fitted for each of the four treatment groups using observed data. The model will include baseline and post-baseline values observed prior to the visit in question as covariates. The estimated parameters, and their variances, from this model are used to impute missing values for subjects in each treatment groups.

For each of the complete 500 datasets, penalty values are added stepwise to the imputed change from baseline at week 40, followed by performing an ANCOVA. The addition of the penalty values and subsequent analysis steps should be repeated with increasing penalty values until a significant result in the corresponding superiority and non-inferiority analyses are no longer significant. The tipping point will occur at the penalty level, at which the magnitude of efficacy reduction in subjects with missing data creates a shift in the treatment effect of semaglutide from being statistically significantly better than dulaglutide to being non-statistically significantly better for the superiority test and similarly for the non-inferiority test. There will be one tipping point per dose level (Sema 0.5 mg vs. Dula 0.75 mg and Sema 1.0 mg vs. Dula 1.5 mg) and hypotheses test (superiority/ non-inferiority), e.g. four estimates in total.

For more technical details, see SPS[6], where also the seeds used when data is generated, can be found.

2.10.2 Sensitivity analyses addressing non-inferiority

In support of non-inferiority testing, the below two sensitivity analyses will be performed. These sensitivity analyses only include a subset of all randomised subjects so the integrity of randomisation may not be maintained. Therefore, while the below two analyses generally are conservative for testing non-inferiority, the inherent risk for bias in any direction cannot be excluded.

- *PP analysis* – the statistical analysis will be the same as the primary MMRM based analysis but it will be based on the PP analysis set and the on-treatment without rescue observation period.

- *Complete case analysis* – includes subjects in the FAS who do not have their endpoint imputed in the primary analysis. The change from baseline in HbA_{1c} at week 40 will be analysed by a linear normal model (analysis of covariance (ANCOVA)) with treatment and country as fixed effects and baseline HbA_{1c} as a covariate.

2.10.3 Other sensitivity analyses

The following secondary estimand will be defined:

- de-facto treatment difference at week 40 for all randomised subjects

This estimand assesses the average effect in a future population that results from treatment with s.c. semaglutide plus antidiabetic rescue medication(s) as compared to treatment with dulaglutide plus antidiabetic rescue medication(s). Interpretation of this estimand depends on whether the use of antidiabetic rescue medication and treatment adherence in this trial reflects clinical practice. The defacto estimand will be estimated from the below analysis:

- *Retrieved dropout analysis* – This in-trial treatment policy analysis will be based on the FAS using the in-trial observation period. Missing data will be imputed within the same group defined, not only by the randomised treatment (semaglutide/ dulaglutide), but also by the status of treatment completion (still on randomised treatment at week 40 yes/no) (8 groups in total). It is hereby assumed that the likely values of what the missing data would have been if available are best described by information from subjects who at week 40 are similar in terms of randomised treatment and treatment completion status. For each group missing values will be imputed using a MCMC method, as described in section 2.10.1. For each of the 500 datasets, an ANCOVA is applied to data from baseline to end-of-treatment, week 40. The model use treatment and country as factors and baseline value as covariate. The estimates and standard deviations for the 500 data sets are pooled to one estimate and associated standard deviation using Rubin's rule[7]. From these pooled estimates the confidence interval for the treatment differences and the associated p-value are calculated.

The last sensitivity analysis will be:

- *Last observation carried forward (LOCF) analysis* – This analysis will be based on the FAS using the on-treatment without rescue observation period with missing data imputed by LOCF. Based on the complete data set, the change from baseline in HbA_{1c} at week 40 will be analysed by a linear normal model (ANCOVA) with treatment and country as fixed effects and baseline HbA_{1c} as a covariate.

2.10.4 Assessment of sensitivity analyses

The results from the sensitivity analysis will be collectively used to interpret the confirmatory trial conclusions on HbA_{1c} and body weight, and in particular evaluate the impact of the MAR assumptions. No absolute criteria will be defined as to when a sensitivity analysis can be defined to have confirmed the robustness of the conclusions. Due to the large number of the sensitivity analyses and their inherent conservative nature, it is not considered a requirement that all confirmatory hypotheses are confirmed across all the sensitivity analyses. The results of the sensitivity analysis will be discussed in the clinical trial report with the aim to use the sensitivity results in totality to evaluate the credibility of the confirmatory trial conclusions.

2.11 Secondary endpoints

2.11.1 Confirmatory secondary endpoint

The confirmatory secondary endpoint is change from baseline to week 40 in body weight (kg). This endpoint will be analysed in the same type of model as the primary endpoint, except with baseline body weight as a covariate instead of baseline HbA_{1c}. From this model the two by dose level estimated treatment differences between semaglutide versus dulaglutide will be presented at week 40 together with associated two-sided 95% confidence intervals and unadjusted two sided p-values. The same sensitivity analyses as pre-specified for testing superiority for the primary HbA_{1c} endpoint will also be performed to evaluate the robustness of the body weight superiority conclusions.

For an overview of statistical analyses to be performed for the confirmatory secondary endpoint, body weight, see Table 3.

Table 3 Summary of sensitivity analyses of body weight

Population	Period	Imputation	Statistical model
FAS	On-treatment without rescue medication	Last observation carried forward for subjects with missing value at week 40	ANCOVA [1)]
FAS	On-treatment without rescue medication	Multiple imputation	Tipping point analysis
FAS	In-trial	Multiple imputation	Retrieved dropout analysis, using an ANCOVA model

[1)] Baseline and week 40 measurements will be used in the analysis

2.11.2 Confirmatory secondary hypothesis

For body weight, the following confirmatory hypothesis will be tested at each dose level comparing; (i) semaglutide 0.5 mg versus dulaglutide 0.75 mg and (ii) semaglutide 1.0 mg versus dulaglutide 1.5 mg with mean treatment difference defined as μ=(semaglutide minus dulaglutide):

- Superiority
  - H_0: μ >=0.0% against H_a: μ <0.0%

Superiority will be considered confirmed if the corresponding two-sided p-value is strictly below its local two-sided significance level as defined by the closed testing procedure in Figure 1.

2.12 Supportive secondary endpoints

2.12.1 Efficacy endpoints

The supportive secondary efficacy endpoints will be presented based on FAS using the on-treatment without rescue observation period as the key observation period with the in-trial observation period being supportive.

Endpoints include change from baseline to week 40 in:

- Relative change in body weight (%)
- FPG*
- SMPG, 7-point profile:
  - Mean 7-point profile, defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time
  - Mean post prandial increment (over all meals)
- Fasting blood lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)
- BMI and waist circumference
- Systolic and diastolic blood pressure*
- Patient reported outcomes
  - SF-36v2™
  - DTSQ*

The above continuous endpoints will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as a covariate. Fasting blood lipids profile endpoints will be log-transformed prior to analysis including also the relevant log-transformed baseline value used as a covariate.

Subjects who after 40 weeks treatment achieve (yes/no)

- HbA_{1c} <7.0% (53 mmol/mol) ADA target
- HbA_{1c} ≤6.5% (48 mmol/mol) AACE target*
- Weight loss ≥5%
- Weight loss ≥10%
- HbA_{1c} <7.0% (53 mmol/mol) without severe or BG confirmed symptomatic hypoglycaemia episodes and no weight gain
- HbA_{1c} reduction ≥1%
- Weight loss ≥3%
- HbA_{1c} reduction ≥1% and weight loss ≥3%

The above eight binary endpoints will be analysed using a logistic regression model with treatment and region as fixed effects and baseline response as covariate (i.e. baseline HbA_{1c} for binary HbA_{1c}

endpoints, baseline weight for weight endpoints and both baseline HbA_{1c} and baseline weight for the binary endpoint that combines both parameters). To account for missing data, the analysis will be made using a sequential multiple imputation approach as described below:

- Multiple imputed data sets (500) will be created in which missing values for the underlying continuous assessments are imputed by treatment group assuming MAR and as described in section 2.7.
- The binary endpoint will be created for each of the 500 complete data sets
- Each of the created complete data set will be analysed with the logistic model and inference will be drawn using Rubin's rule [7].

PRO outcomes

The PRO outcomes endpoints that will be analysed at week 40 are:

- PRO questionnaire outcome DTSQs (individual items and treatment satisfaction score (6 of the 8 items summed)), and
- PRO questionnaire outcome SF-36v2™

The above continuous endpoints will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as a covariate.

7-point profile (SMPG)

Subjects will be asked to perform SMPG measurements before and 90 minutes after breakfast, lunch, dinner, respectively, and at bedtime.

The endpoints from the 7-point profiles that will be analysed at week 40 are:

- Mean of the 7-point profile, defined as the area under the profile, calculated using the trapezoidal method, divided by the measurement time
- Mean increment over all meals

The mean of the 7-point profile and the mean of the post prandial increments at week 40 will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as a covariate.

2.12.2 Safety endpoints

All safety endpoints will be evaluated based on SAS and the on-treatment observation period as the primary observation period with the in-trial observation period being supportive if not otherwise specified.

The following endpoints are used to support the safety objectives:

- Number of TEAEs
- Number of treatment emergent severe or BG confirmed symptomatic hypoglycaemia episodes
- Treatment emergent severe or BG confirmed symptomatic hypoglycaemia (yes/no)

Change from baseline to week 40 in:

- Lipase
- Amylase
- Pulse

The above continuous endpoints will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as covariate. Lipase and amylase endpoints will be log-transformed prior to analysis including also the relevant log-transformed baseline value as covariate.

The following laboratory assessments will be summarised descriptively:

- Haematology
- Biochemistry
- Calcitonin

The following categorical safety evaluations will be summarised descriptively:

- ECG category
- Physical examination

Calcitonin

In addition to the continuous summaries, calcitonin will be displayed in terms of the number of subjects (N), the percentage of subjects (%) and the event rate per 100 years of exposure (R). The below criteria are defined for categorical tabulations. Summaries will be presented for all subjects and by gender.

- Persistent (all post baseline measurements)
- From < upper normal limit (UNL) to persistently ≥ UNL
- From <UNL to persistently ≥1.5 UNL
- From <UNL to persistently ≥20 ng/L
- From <UNL to persistently ≥50 ng/L
- From <20 ng/L to persistently ≥20 ng/L
- From <50 ng/L to persistently ≥50 ng/L

2.12.3 Adverse Events

All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding.

A TEAE is defined as an AE with onset in the on-treatment period (see definition of observation period in section 2.6).

TEAEs will be summarised in terms of the number of subjects with at least one event (N), the percentage of subjects with at least one event (%), the number of events (E) and the event rate per 100 patient years of observation time (R) for the on-treatment observation period. Supportive summaries of AEs will be made for the in-trial observation period.

Classification of Hypoglycaemia:
Hypoglycaemic episodes will be summarised for the SAS and the on-treatment observation period. No supportive summaries will be made based on the in-trial observation period and episodes with onset date after the on-treatment observation period will be reported in listings only.

Treatment emergent: hypoglycaemic episodes will be defined as treatment emergent if the onset is in the on-treatment period (see definition of observation period in section 2.6)

Nocturnal hypoglycaemic episodes: are episodes occurring between 00:01 and 05.59 both inclusive.

Hypoglycaemic episodes are classified according to the Novo Nordisk classification of hypoglycaemia (see Figure 2) and the ADA classification of hypoglycaemia (see Figure 3).

Novo Nordisk classification of hypoglycaemia
In normal physiology, symptoms of hypoglycaemia occur below a plasma glucose level of 3.1 mmol/L (56 mg/dL) [8]. Therefore, Novo Nordisk has included hypoglycaemia with plasma glucose levels below this cut-off point in the definition of BG confirmed hypoglycaemia.

Novo Nordisk uses the following classification (see Figure 2) in addition to the ADA classification:

- Severe or BG confirmed symptomatic hypoglycaemia: An episode that is severe according to the ADA classification[9] or BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycaemia.

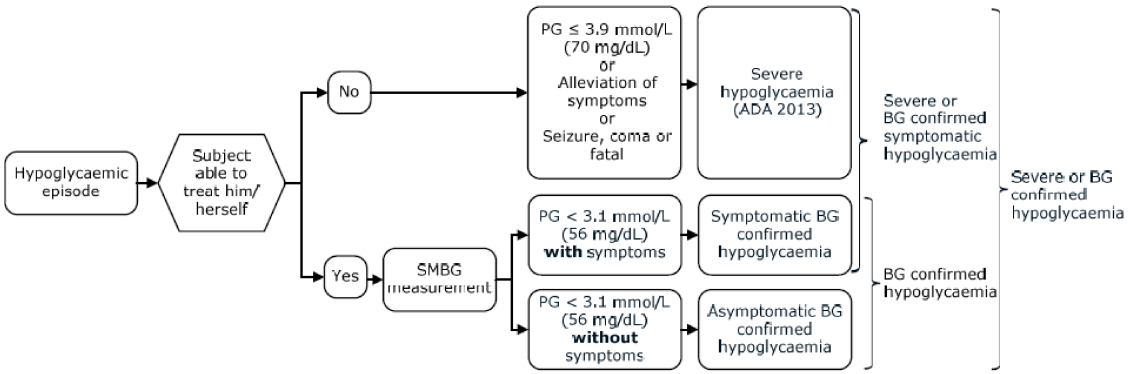

Figure 2 Novo Nordisk classification of hypoglycaemia

ADA classification[9] of hypoglycaemia

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 3.9 mmol/L (70 mg/dL) but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 3.9 mmol/L (70 mg/dL).

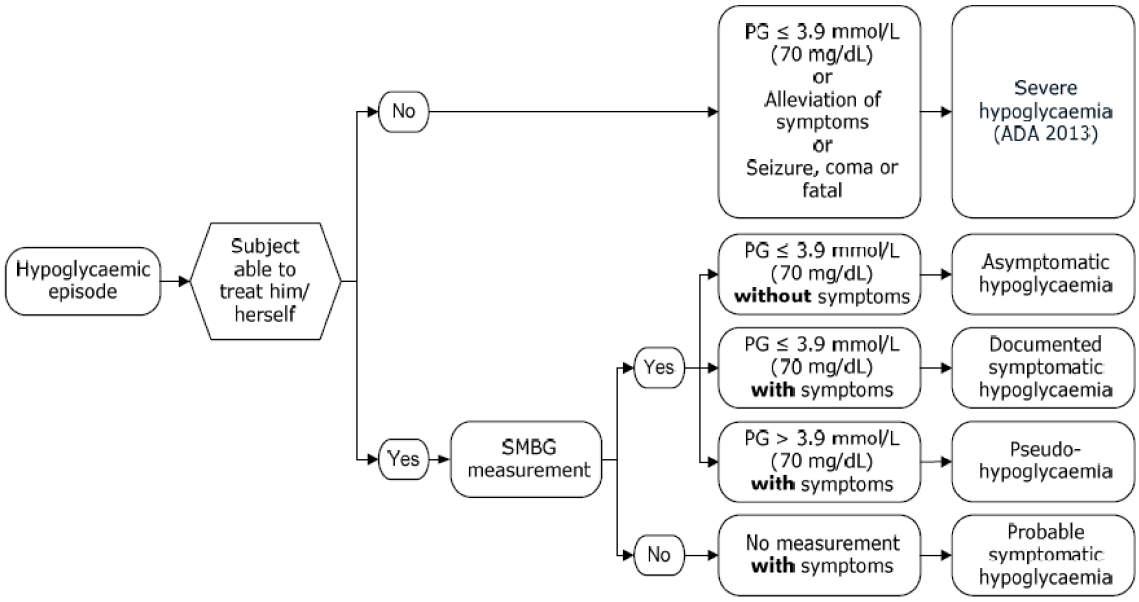

Figure 3 ADA classification of hypoglycaemia

Data on treatment emergent hypoglycaemic episodes are presented in terms of the number of subjects with at least one episode, the percentage of subjects with at least one episode (%), the total number of episodes and the episode rate per 100 years of exposure. Summaries of treatment emergent hypoglycaemic episodes will be presented as an overview including all episodes and episodes by severity.

Number of severe or BG confirmed symptomatic hypoglycaemic episodes

The number of treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using a negative binomial regression model with a log-link function and the logarithm of the time period covered by the subject's on-treatment observation period as offset. The model will include factors for treatment and region as fixed factors and baseline HbA_{1c} as covariate.

Severe or BG confirmed symptomatic hypoglycaemic episodes (yes/no)

The binary endpoint indicating whether a subject has at least one treatment emergent severe or BG confirmed symptomatic hypoglycaemic episodes will be analysed using a logistic regression model with treatment and region as fixed factors and baseline HbA_{1c} as covariate.

2.13 Health economics and/or patient reported outcomes

The PRO questionnaires, SF-36v2™ and DTSQs, derived endpoints for overall scores and domains will be analysed separately using a similar model as for the primary endpoint but with the associated baseline value as covariate.

3 Changes to the statistical analyses planned in the protocol

The main analyses were described in the protocol for trial NN9535-4216. More detailed descriptions of endpoints and analyses are provided in this SAP. Only key changes and major additions to the protocol are described below.

Changes from protocol NN9535-4216:

- 'and considered supportive of efficacy evaluations' has been deleted in section 2.6 "Data selections and observations periods". No efficacy evaluation will be done in the 'On-treatment' observation period.
- To get an overview of statistical analyses to be performed for the primary (HbA1c) and confirmatory secondary (body weight) endpoints, table 2 and table 3 have been added in respective section, 2.7 and 2.11.
- Pattern-mixture model using multiple imputation addressing both non-inferiority and superiority has been deleted. A pattern-mixture model using multiple imputation a 'Tipping point analysis' will be performed instead of the comparator-based analysis described in protocol. See section 2.10.1.
- To evaluate the robustness of the primary analyses, a 'Retrieved dropout analysis', described in section 2.10.3, will be performed instead of the 'In-trial analysis', which was stated in the protocol.
- Relative change from baseline in body weight has been added in section 2.12.1.
- Number of multiple imputed data sets has been changed from 100 to 500, see section 2.12.1.
- "(nominal alpha=0.05)" in section 2.4, 2.7, 2.9 and 2.11.2 has been deleted to avoid confusion. The overall significance level is α=0.05 (two-sided).

4 References

1. Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009; 28(4):586-604.
2. Rohmeyer, K. and Klinglmueller, F. gMCP: Graph Based Multiple Test Procedures. R package version 0.8-8. 3 Oct 2014.
3. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1). EMA . 2 Jul 2010.
4. National Academy of Sciences (NAS). The Prevention and Treatment of Missing Data in Clinical Trials. Washington D.C.: The National Academies Press, 2010.
5. Xu Yan , Shiowjen Lee & Ning Li (2009) Missing Data Handling Methods in Medical Device Clinical Trials, Journal of Biopharmaceutical Statistics, 19:6, 1085-1098, http://dx.doi.org/10.1080/10543400903243009
6. 4216 Statistical Programming Specification, novoDOCs ID number: 003660253
7. Little RJA, Rubin DB. Statistical analysis with missing data. New York: John Wiley & Sons, 1987.
8. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counter regulatory systems are higher than the threshold for symptoms. J Clin Invest 1987; 79(3):777-781.
9. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013; 36(5):1384-1395.