Cover Page for Statistical Analysis Plan

Sponsor name:	Novo Nordisk A/S
NCT number	NCT04560998
Sponsor trial ID:	NN9535-4533
Official title of study:	Effect of semaglutide on functional capacity in patients with type 2 diabetes and peripheral artery disease
Document date*:	26 August 2024

*Document date refers to the date on which the document was most recently updated.

Statistical Analysis Plan

Trial ID: NN9535-4533

Effects of semaglutide on functional capacity in patients with type 2 diabetes and peripheral arterial disease

Redacted statistical analysis plan
Includes redaction of personal identifiable information only.

[redacted]
Biostatistics GLP-1 Diabetes

Table of contents

Page

Table of tables

Page

Version history

This Statistical Analysis Plan (SAP) for trial NN9535-4533 is based on the protocol version 7.0 dated 18Apr2023. The first version of the SAP is final before first patient first visit.

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale

3.0		• Handling issues in the imputation model (Section 5.3.2)
		  • Null walking distance at week 26 will be replaced by a negligible non-zero value (10^{-3} m).
		  • Increasing number of iterations in EM algorithm
		• Follow-up treadmill assessments (hypothetical estimand) based on treatment completion status at week 52 instead of on-treatment without rescue medication period (Section 5.4.1.2)
		• Sensitivity Analysis – Handling treadmill assessments >7 weeks between week 52 and week 57 (Section 5.4.1.3)
		• Additional subgroups by region, age groups and sex
		  • for analysing maximum walking distance at week 52 (Section 5.7.3)
		  • for summarising SAEs (Section 5.6.2)
			As log(0) is not defined, assign 10^{-3} m such that it would be the least walking distance amongst all observed distances
			To ensure convergence of both ML estimates and Posterior mode is achieved in EM-algorithm
			To ensure suitable observation period is considered for the analysis as patients will not be on the treatment at week 57.
			To ensure the follow-up treadmill assessment is carried out within the window of ≤ 7 weeks
			To evaluate the consistency of the treatment effect across subgroups
			To summarise distribution of events across subgroups

SAP Version	Approval Date	Change	Rationale
		• ABI and TBI analysis – Ratio to baseline at week 52 • Responder analysis for both maximum walking distance and VascuQoL-6 total score based on meaningful-within patient change (MWPC) thresholds (Section 5.7.2) • Analysis on time to first occurrence of major adverse limb events [MALE] (Section 5.7.4) • WIQ total score – best & worst case scenarios (Section 6.3.2)	The endpoints will be log-transformed, and analysis will be carried out producing estimated treatment ratio (ETR) with its CI To evaluate the clinical relevance of the treatment effect, once superiority is confirmed To explore the effect of Semaglutide 1.0 mg in reducing the incidence of MALE events To describe the derivation of best- & worst- case total scores for WIQ in the presence of missing items
2.0	11SEP2023	Updated based on protocol amendment v7.0.	• The supportive endpoint "Follow-up change in maximum walking distance on a constant load treadmill test" is elevated to confirmatory secondary endpoint with the purpose of ensuring that the follow-up period results are taken into consideration by regulators • The inversion of confirmatory endpoints "Change in pain-free walking distance on a constant load treadmill test" and "Change in Vascular Quality of Life Questionnaire-6 (VascuQoL-6) score"
1.0	18SEP2020	Not Applicable	First version

1 Introduction

This Statistical Analysis Plan (SAP) describes in detail the analyses of efficacy, safety and other endpoints and assessments in trial NN9535-4533. Endpoints and assessments in the trial are listed in section 6.3 and Appendix 3.

Details regarding summary tables, figures and listings (TFL) will be specified in a separate document (mock TFL).

1.1 Objectives and endpoints

The objectives and estimands in the trial are described below.

1.1.1 Primary objective and estimands

The primary objective is to demonstrate the effect of s.c. semaglutide 1 mg once-weekly on walking ability compared with placebo, both added to standard-of-care, in patients with T2D and PAD with intermittent claudication.

The primary estimand will be the median treatment ratio to baseline at week 52 in maximum walking distance for semaglutide 1 mg versus placebo, both as add-on to standard-of-care, in all randomised patients, regardless of change in background medication, rescue treatment (e.g. revascularisation or starting cilostazol/pentoxifylline), and adherence to randomised treatment. A composite strategy is used to handle intercurrent events of death, and physical inability to perform the treadmill test. These intercurrent events are incorporated into the outcome by ascribing them an extreme unfavourable rank.

Two secondary estimands for the primary objective will be the median treatment ratio to baseline (i) at week 57 in maximum walking distance and (ii) at week 52 in pain free walking distance for semaglutide 1 mg versus placebo, both as add-on to standard-of-care, in all randomised patients, regardless of change in background medication and adherence to randomised treatment. The rationale for the pain free walking distance estimand is that the pain-free walking distance is of particular importance to the patient, who is reminded of his disease in the moment pain is experienced.

The primary and secondary estimands for the primary objective are listed in Table 2 below.

Table 2 Primary and secondary estimands for the primary objective

Objective	Estimand category	Estimand
Primary objective:	**Primary**	**Treatment condition:** Semaglutide 1 mg or placebo, regardless of adherence to randomised treatment and initiation of rescue treatment **Variable/Endpoint:** Ratio to baseline in maximum walking distance at week 52 **Population of interest:** All randomised **Intercurrent event strategy:** Events of death or physical inability to perform the treadmill test, are incorporated into the outcome by ascribing them an extreme unfavourable rank (composite) Interventions and medications related to worsening of PAD (rescue treatment): "regardless of initiation of rescue treatment" (treatment policy) **Population-level summary measure:** Median ratio of Semaglutide 1 mg vs placebo

Objective	Estimand category	Estimand
To demonstrate the effect of s.c. semaglutide 1 mg once-weekly on walking ability compared with placebo, both added to standard-of-care, in patients with T2D and PAD with intermittent claudication	**Secondary 1[a]**	**Treatment condition:** Semaglutide 1 mg or placebo, had all patients adhered to randomised treatment and not received rescue treatment **Variable/Endpoint:** Ratio to baseline in maximum walking distance at week 52 **Population of interest:** All randomised **Intercurrent event strategy:** Discontinuation of trial product: "had the patient not discontinued treatment" (hypothetical) Interventions and medications related to worsening of PAD (rescue treatment): "had rescue treatment not been available" (hypothetical) Events of death or physical inability to perform the treadmill test: "had the patient not died or been unable to perform the test" (hypothetical) **Population-level summary measure:** Geometric mean ratio of semaglutide 1 mg vs placebo
	Secondary 2	**Treatment condition:** Semaglutide 1 mg or placebo, regardless of adherence to randomised treatment and initiation of rescue treatment **Variable/Endpoint:** Ratio to baseline in maximum walking distance at week 57 **Population of interest:** All randomised **Intercurrent event strategy:** Events of death or physical inability to perform the treadmill test, are incorporated into the outcome by ascribing them an extreme unfavourable rank (composite) Interventions and medications related to worsening of PAD (rescue treatment): "regardless of initiation of rescue treatment" (treatment policy) **Population-level summary measure:** Median ratio of Semaglutide 1 mg vs placebo
	Secondary 3	**Treatment condition:** Semaglutide 1 mg or placebo, had all patients adhered to randomised treatment and not received rescue treatment **Variable/Endpoint:** Ratio to baseline in maximum walking distance at week 57 **Population of interest:** All randomised **Intercurrent event strategy:** Discontinuation of trial product: "had the patient not discontinued treatment" (hypothetical) Interventions and medications related to worsening of PAD (rescue treatment): "had rescue treatment not been available" (hypothetical) Events of death or physical inability to perform the treadmill test: "had the patient not died or been unable to perform the test" (hypothetical) **Population-level summary measure:** Geometric mean ratio of semaglutide 1 mg vs placebo

Objective	Estimand category	Estimand
	Secondary 4	**Treatment condition:** Semaglutide 1 mg or placebo, regardless of adherence to randomised treatment and initiation of rescue treatment **Variable/Endpoint:** Ratio to baseline in pain free walking distance at week 52 **Population of interest:** All randomised **Intercurrent event strategy:** Events of death or physical inability to perform the treadmill test, are incorporated into the outcome by ascribing them an extreme unfavourable rank (composite) Interventions and medications related to worsening of PAD (rescue treatment): "regardless of initiation of rescue treatment" (treatment policy) **Population-level summary measure:** Median ratio of semaglutide 1 mg vs placebo
	Secondary 5[a]	**Treatment condition:** Semaglutide 1 mg or placebo, had all patients adhered to randomised treatment and not received rescue treatment **Variable/Endpoint:** Ratio to baseline in pain free walking distance at week 52 **Population of interest:** All randomised **Intercurrent event strategy:** Discontinuation of trial product: "had the patient not discontinued treatment" (hypothetical) Interventions and medication related to worsening of PAD (rescue treatment): "had rescue treatment not been available" (hypothetical) Events of death or physical inability to perform the treadmill test: "had the patient not died or been unable to perform the test" (hypothetical) **Population-level summary measure:** Geometric mean ratio of semaglutide 1 mg vs placebo

Notes: [a] Not related to the confirmatory hypotheses.

1.1.2 Secondary objectives and estimands

The secondary objectives are to compare the effect of s.c. semaglutide 1 mg once-weekly versus placebo, both added to standard-of-care in patients with T2D and PAD with intermittent claudication with regards to:

- Patient reported symptoms and impacts of intermittent claudication (VascuQoL-6[1])
- Body weight
- HbA_{1c}
- Lipids
- Blood pressure
- Non-invasive blood pressure indices (ankle-brachial index (ABI), toe-brachial index (TBI))
- Safety
- Patient-reported walking ability (WIQ[2])
- Patient reported health-related quality of life (SF-36[3]))

The estimands related to the confirmatory secondary endpoint are described in Table 3

Table 3 Estimands for the confirmatory secondary endpoint

Objective		Estimand category	Estimand
Secondary objective: To compare the effect of s.c. semaglutide 1 mg once-weekly versus placebo, both added to standard-of-care in patients with T2D and PAD with intermittent claudication with regards to disease specific patient reported outcome		**Secondary 1**	**Treatment condition:** Semaglutide 1 mg or placebo, regardless of adherence to randomised treatment and initiation of rescue treatment **Variable/Endpoint:** Change from baseline in VascuQoL-6 at week 52 **Population of interest:** All randomised **Intercurrent event strategy:** Events of death are incorporated into the outcome by ascribing them an extreme unfavourable rank (composite) Interventions and medications related to worsening of PAD (rescue treatment): "regardless of initiation of rescue treatment" (treatment policy) **Population-level summary measure:** Median difference between Semaglutide 1 mg vs placebo
		Secondary 2[a]	**Treatment condition:** Semaglutide 1 mg or placebo, had all patients adhered to randomised treatment and not received rescue treatment **Variable/Endpoint:** Change from baseline in VascuQoL-6 at week 52 **Population of interest:** All randomised **Intercurrent event strategy:** Discontinuation of trial product: "had the patient not discontinued treatment" (hypothetical) Interventions and medication related to worsening of PAD (rescue treatment): "had rescue treatment not been available" (hypothetical) Events of death: "had the patient not died" (hypothetical) **Population-level summary measure:** Mean difference between Semaglutide 1 mg vs placebo

Notes: [a] Not related to the confirmatory hypotheses

1.1.3 Exploratory objective

The exploratory objective is to compare the effects of s.c. semaglutide 1 mg once-weekly versus placebo, both added to standard-of-care in patients with T2D and PAD with intermittent claudication with regards to:

- Daily activity levels (wrist worn activity tracker)

1.2 Trial design

The trial is a 52-week, randomised, double-blind, placebo-controlled trial comparing s.c. semaglutide 1 mg versus placebo both added to standard-of-care and administered once-weekly in patients with T2D and PAD with intermittent claudication.

Patients will be randomised in a 1:1 ratio to receive either s.c. semaglutide 1 mg or placebo as add-on to standard-of-care.

The screening period is up to 3 weeks before randomisation. The treatment duration is 52 weeks including an eight weeks escalation period. The follow-up period is 5 weeks.

In addition to the main study, an evaluation of daily activity level will be performed in a subset of patients using a wrist-worn activity tracker to quantify the level of activity in selected time periods of the study.

An external event adjudication committee (EAC) will perform ongoing adjudication of predefined CV events and other selected AEs in an independent and blinded manner.

There are no planned interim analyses.

2 Statistical hypotheses

For the primary endpoint, ratio to baseline in maximum walking distance at week 52, the following confirmatory one-sided hypothesis is planned to be tested. Let the median ratio to baseline for semaglutide 1 mg and placebo be defined as M_{sema} and $M_{placebo}$, respectively. Superiority for the maximum walking distance at week 52 will then be tested as:

$$H_0: M_{sema} \leq M_{placebo} \text{ against } H_a: M_{sema} > M_{plac}$$

Operationally the hypotheses will be evaluated by two-sided tests.

The hypothesis for the confirmatory secondary endpoint, ratio to baseline in maximum walking distance at week 57 and pain free walking distance at week 52, is the same as for the primary endpoint. Likewise, the hypothesis for the confirmatory secondary endpoint, change from baseline in Vascu-Qol-6 score at week 52, is the same as for the primary endpoint, except that M denotes median change from baseline.

Multiplicity Adjustment

The following hierarchical testing strategy will be applied to control the type-I error at an overall alpha level (two-sided) of 0.05 across the confirmatory endpoints:

1. Superiority of semaglutide 1 mg vs. placebo on ratio to baseline (week 0) at week 52 in maximum walking distance
2. Superiority of semaglutide 1 mg vs. placebo on ratio to baseline (week 0) at week 57 in maximum walking distance
3. Superiority of semaglutide 1 mg vs. placebo on change from baseline (week 0) to week 52 in VascuQoL-6 score
4. Superiority of semaglutide 1 mg vs. placebo on ratio to baseline (week 0) at week 52 in pain-free walking distance

As per the hierarchical strategy, each null hypothesis will be considered for confirmatory testing only where all previous null hypotheses have been rejected in favour of semaglutide 1 mg.

3 Sample size determination

The primary endpoint is ratio to baseline (week 0) at week 52 in maximum walking distance on a constant-load treadmill test. The confirmatory secondary endpoints are ratio to baseline (week 0) at week 57 in maximum walking distance, change from baseline (week 0) to week 52 in VascuQoL-6 score and ratio to baseline (week 0) at week 52 in pain-free walking distance. Superiority will be tested for all four endpoints. The type-I error rate will be controlled in the strong sense across the primary and the confirmatory secondary hypotheses at an overall alpha level (two-sided) of 0.05 as described above.

The trial is designed to have 89% power to be able to detect a 20% improvement in maximum walking distance at week 52 compared to baseline for semaglutide 1 mg relative to placebo, hence confirm superiority for the primary endpoint. This effect size is expected to be clinically relevant (evaluated by the PGI-S) and is considered achievable due to the potential mode-of-action of semaglutide.

Primary endpoint

The power has been calculated using stochastic simulation. First, a complete dataset has been simulated using a normal distribution for the log-transformed primary endpoint.

Treatment ratio (semaglutide 1 mg versus placebo) is assumed to be 1.2, the coefficient of variation to be 0.8 and a 1:1 randomisation. There is some uncertainty over the coefficient of variation but based on results from the cilostazol trials (by dividing the standard deviation with the mean)[4-6] an assumption of a coefficient of variation of 0.8 seems plausible.

Missing observations due to death (2% in total corresponding to 8 deaths in each treatment group), inability to perform the treadmill test (3% in total corresponding to 12 cases in each treatment group), and due to other reasons (3% in total corresponding to 12 cases in each treatment group), have been introduced in the complete dataset, assuming equal distribution between treatment groups.

First, log-transformed endpoints that are missing due to other reasons than death or inability to perform the walking test are imputed by sampling from a normal distribution corresponding to the theoretical distribution in the placebo arm. Second, the resulting imputed dataset is analysed using Wilcoxon rank-sum-test, where ranks are assigned as follows: Patients with non-missing observations are assigned ranks according to the observed endpoint. Patients with missing observation due to death or physical inability to perform the treadmill test are assigned ranks as described in Section 5.3.2. Third, the imputed standardized Wilcoxon test statistics are combined using Rubin's rule to obtain a P-value.

Repeating the simulation 5,000 times, each with 50 imputations, 800 patients must be randomised to obtain 89% power for confirming superiority for the primary endpoint.

Secondary confirmatory endpoints

The same assumptions as for the primary endpoint are made for ratio to baseline (week 0) at week 57 in maximum walking distance and ratio to baseline (week 0) at week 52 in pain-free walking distance. The treatment ratio of 1.2 is likewise expected to be achievable due to the mode of actions of semaglutide. Therefore, with 800 randomised patients there is a marginal power of 89% for confirming superiority for this secondary confirmatory endpoint.

For change from baseline (week 0) to week 52 in VascuQoL-6 score, the power for confirming superiority is calculated similar to the power for the primary endpoint. Stochastic simulation based on an assumption of a treatment difference of 2 points and a standard deviation of 5 are assumed based on earlier trials.[7]

Missing observations (8%) in total have been introduced in the simulated complete dataset in the same way as for the primary endpoint. The resulting imputed dataset is analysed using a Wilcoxon rank-sum-test with ranks assigned using the same algorithm for the primary endpoint and combined using Rubin's rule to obtain a p-value. Repeating the simulation 5,000 times, each with 50 imputations, with 800 randomised patients, the power is >99% for confirming superiority of VascuQoL-6 score.

Overall power

The joint (effective) power is calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively. Since some of these endpoints/tests are positively correlated, the assumption of independence is viewed as conservative.

With the above assumptions, 89% power for confirming superiority for the primary endpoint will require a total of 800 randomised patients (400 patients randomised in each treatment group), when comparing semaglutide 1 mg to placebo.

Table 4 summarises the assumptions for the sample size calculation and provides an overview of the marginal and joint power for each hypothesis.

Table 4 Assumptions used in sample size calculation and power for meeting individual hypotheses as well as joint power

Endpoint	Hypothesis	Assumptions	Randomised patients	Marginal power	Joint power
Maximum walking distance	Superiority	Treatment ratio = 1.2 Coefficient of variation = 0.8	800	89%	89%
VascuQoL-6 score	Superiority	Treatment difference = 2-points Standard deviation = 5	800	> 99%	~89%
Pain-free walking distance	Superiority	Treatment ratio = 1.2 Coefficient of variation = 0.8	800	89%	~79%

Abbreviations: VascuQoL-6: Vascular Quality of Life-6. Each scenario assumes 2% (8 per treatment arm) dead; 3% unable to perform walking test (walking test endpoints only, 12 per treatment arm); 3% missing due to other reasons (12 per treatment arm).

The sample size calculations above are sensitive to the assumptions made for the true treatment ratio for the primary endpoint. Table 5 illustrates this with six alternative set of assumptions.

Table 5 Power with different assumptions for the treatment ratio for the primary endpoint

Treatment ratio	Coefficient of variation	Power obtained with 800 randomised patients
1.2	0.8	89%
1.2	1.0	77%
1.2	1.5	53%
1.3	0.8	>99%
1.3	1.0	98%
1.3	1.5	85%

Approximately 1,143 patients will be screened to achieve 800 patients (screening failure rate of 30% is anticipated) randomly assigned to trial product.

4 Analysis sets

Data selection for statistical analyses will be a two-step process, first selecting patients based on the analysis population and subsequently events/data for those patients based on the observation period, see Table 6 and Table 7 for definitions of analysis populations and observation periods, respectively.

Table 6 Analysis populations

Population	Description
Randomised	All patients randomised
Full analysis set	Full analysis set (FAS): All patients randomised. Patients will be analysed according to the randomised treatment
Safety analysis set	All patients randomly assigned to trial treatment and who take at least 1 dose of trial product. Patients will be analysed according to the trial product received for the majority of the period they were on treatment

Table 7 Observation periods

<table>
<tr><th>Observation period</th><th colspan="2">Description</th></tr>
<tr><td>In-trial</td><td colspan="2">This observation period is defined as the period from the date of randomisation to the first of the following dates, both inclusive:
• Date of the end-of-trial (follow-up) visit (V9)
• Date of death
• Date when patient withdrew informed consent
• Date of last contact for patients lost to follow-up</td></tr>
<tr><td rowspan="4">On-treatment</td><td colspan="2">This observation period includes assessments and events for the time period where patients are exposed to the investigational medicinal products, regardless of whether the patients have received rescue treatment or not, as well as baseline assessments.
The observation period starts at the date of first dose of trial product. The observation period and ends at the first of the dates listed below by type of endpoint.</td></tr>
<tr><td>Adverse events (other than severe hypoglycaemic episodes)</td><td>Efficacy, severe hypoglycaemic episodes and all other endpoints</td></tr>
<tr><td>• Date of the end-of-trial (follow-up) visit (V9)
• Date of premature end-of-trial (follow-up) visit (V9A)
• Date of last dose on investigational trial product + 42 days
• End date of the ‘in-trial’ observation period</td><td>• Date of last dose on investigational trial product + 7 days</td></tr>
<tr><td colspan="2">For the adverse events the rationale for the end of the on-treatment period related to last date on trial product is the time of follow-up at 5 weeks (35 days) after the last date on trial product, which is corresponding to approximately five half-lives of semaglutide OW and including the visit window of 7 days. In total 42 days.
For all other endpoints the on-treatment observation period reflects the period in which patients are treated and includes the visit window of 7 days.
The on-treatment observation period will <u>not</u> account for temporary trial product discontinuations.</td></tr>
</table>

Observation period	Description
On-treatment without rescue treatment	This observation period includes assessments and events for the time period where patients were exposed to trial product and before rescue treatment. Thus, this observation period is a subset of the on-treatment period; excluding observations at and following rescue treatment. The definition of rescue treatment can be seen in the protocol section 6.5.1. The date of rescue treatment will be the first date of the following: • Date of medication taken due to worsening of the PAD • Date of artery revascularisation procedure

Data points collected outside an observation period (not fulfilling the criteria for the period) will be treated as missing in the analysis. Baseline data will always be included in an observation period.

Before data are locked for statistical analysis, a review of all data will take place. In general patients should not be excluded from an analysis set and observations should not be excluded from an observation period, if they fulfil the criteria. If patients or observations are excluded, the reasons for their exclusion must be documented before database lock and described in the clinical trial report. Any decision to exclude either a patient or single observation from the statistical analysis is the joint responsibility of the members of the Novo Nordisk study group.

5 Statistical analyses

5.1 General considerations

Novo Nordisk will be responsible for the statistical analysis and reporting. Analysis and reporting will be based on pooled data from all sites and will be performed on un-blinded data after database release.

Where applicable, the comparison presented from a statistical analysis will be semaglutide 1.0 mg versus placebo and results will be presented by the estimated treatment contrast with associated two-sided 95% confidence intervals and p-values corresponding to two-sided tests of no difference.

Unless otherwise mentioned, baseline assessment is defined as the latest available measurement from the randomisation visit (V2) or the screening visit (V1). Thus, if a V2 assessment is missing then the assessment from V1 will be used as the baseline assessment, if available. For the endpoint 'maximum walking distance', the baseline assessment is defined as the mean of the two assessments from the randomisation visit (V2). If only one of the assessments is available, this will be used as the baseline assessment, and if no assessments are available at V2 then the assessment at V1 will be used.

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

All continuous variables will be summarized with n, mean, standard deviation, median, geometric mean, CV, min and max. When relevant number of values n<LLOQ and n>ULOQ will also be presented.

5.2 Subject disposition

The number of patients completing the trial will be summarised by treatment group. The number of patients with premature treatment discontinuation and trial withdrawals will be summarised by treatment group and reason for premature discontinuation and trial withdrawal.

5.3 Primary endpoint analyses

5.3.1 Definition of endpoint

The primary endpoint is ratio to baseline (week 0) at week 52 in maximum walking distance on a constant-load treadmill.

The maximum walking distance on the treadmill will be measured in meter or feet. The measurements in feet will be converted to meters. The logarithm of the values in meters will be used to calculate change from baseline, and when back transformed this will give the ratio to baseline in maximum walking distance. Log transformation has been chosen in the primary analysis to reduce the variability and the impact of extreme values, as described in the cilostazol trials.[4-6]

5.3.2 Main analytical approach

Primary estimand

According to the primary estimand (see Section 1.1.1), the primary analysis will be based on all randomised patients (full analysis set) and the in-trial observation period and, as per the composite strategy for handling intercurrent events, patients with missing values at 52 weeks due to death or physical inability to perform the walking test, will be handled by ascribing them an extreme unfavourable rank.

Specifically, ranks for the primary endpoint will be assigned as follows:

1. Patients with missing values due to death are ordered by time of death (the earlier death, the worse rank)
2. Patients with missing values for the treadmill test due to being physically unable to perform the test are ranked more favourably than all deaths, and ordered by the walking distance at baseline (a higher baseline value corresponds to a greater deterioration and so is assigned a worse rank)
3. Patients with observed values or missing values due to other reasons than death or inability to perform the walking test, are ranked more favourably than all deaths or patients unable to perform the walking test, and ordered according to their actual or imputed value, see below (the lower the walking distance relative to baseline, the worse rank)

The maximum walking distance will be log-transformed, and the analysis will be based on difference between the log transformed value at week 52 and baseline. Any maximum walking distances recorded as zero meters at week 52, will be handled as missing and ranked according to 2) above. Any maximum walking distances recorded as zero meters at week 26, will be handled by assigning a small value of 10^{-3} meters as log(0) is not defined. This also ensures that these walking distances are differentiated from the observed values and are ranked more favourably than category 1 and 2 above but less favourably as compared to those patients who have performed the assessment.

For patients in category 3 above data will be represented numerically as the log transformed primary endpoint for patients with observed data at week 52. Values for patients in category 1 or 2 will be represented numerically as the value -10^5+100 for the missing observation with lowest rank, the value $-10^5+2\cdot100$ for the observation with next-lowest rank and so forth, in accordance with the ranking approach described above. This will ensure that:

1. all extreme unfavourable values are below any observed or imputed value
2. the difference between an extreme unfavourable value and any other value will fall outside the range of differences between any two observed or imputed values

Patients with missing values for the primary endpoint due to other reasons than death or inability to perform the walking test will have their values imputed using multiple imputation under a missing at random (MAR) assumption. Imputation will be performed separately within groups defined by randomised treatment and treatment status at week 52, for a total of four groups: (i) semaglutide/on-treatment; (ii) semaglutide/off-treatment; (iii) placebo/on-treatment; (iv) placebo/off-treatment. First, intermittent missing values are imputed Markov Chain Monte Carlo (MCMC) to obtain a monotone missing data pattern, generating 500 complete data sets. Second, sequential conditional linear regression will be used to impute monotone missing values, starting with the first visit after

baseline and sequentially continuing to the last planned visit at week 52. The regression model used for imputation will include baseline and post-baseline values for the endpoint observed prior to the visit in question as covariates.

Table 9 summarises the handling of missing and observed values for the primary analysis.

If the EM algorithm fails to converge after 200 iterations at either E-step or M-step, the number of iterations will be increased to ensure convergence of both the Maximum Likelihood Estimates (MLE) and posterior mode using MAXITER option in PROC MI.

The 500 complete data sets will be analysed using a Wilcoxon rank-test. Rubin's rule will be used to combine the standardised Wilcoxon test statistics. The confirmatory statistical testing will be based on the p-value from the pooled standardised Wilcoxon test statistic.

Superiority is considered confirmed if the p-value is strictly below 0.05.

For estimation of effect in relation to the primary estimand, the Hodges-Lehmann estimator will be calculated on log-transformed data for each of the 500 complete data sets. Rubin's rule will be used to obtain inferences. Results will be back transformed to original scale, thus showing the median treatment ratio of the ratio to baseline in maximum walking distance and 95% confidence intervals. The approach to numerically representing the data described above will ensure that the estimate and 95% confidence interval are not affected by the specific numerical representation of extreme unfavourable values.

Table 8 Variables used in the analysis of primary endpoint

Variable	Categories
Treatment	SEMAGLUTIDE 1.0 MG PLACEBO
Chg	It is the difference between the log transformed value at week 52 and baseline

A SAS code template for hypothesis testing for Semaglutide 1.0 mg vs Placebo is given below:

```
proc npar1way wilcoxon hl data= <dataset name>;
class treatment;
var chg;
ods output WilcoxonTest=<output dataset name1>  WilcoxonScores=<output dasetname2>
HodgesLehmann=<output dataset name3>; run;
```

Hodges-Lehmann asymptotic estimate of the location shift and its associated 95% confidence limits are calculated using the HL option of the NPAR1WAY procedure.

Table 9 Handling of missing and observed values for the primary estimand/analysis

Assessment at week 52	Patients on randomised treatment at week 52?	Type description	Handling
Available	Yes	**Available on randomised treatment** Patients with a week 52 assessment and on randomised treatment	Use observed value
	No	**Available but discontinued** Patients who discontinued treatment prematurely but returned to have a week 52 assessment	Use observed value
Missing	Yes	**Physically unable to perform walking test on randomised treatment** Patients on randomised treatment but without a week 52 assessment due to inability to perform walking test	Incorporate into endpoint (composite strategy)
		Missing on randomised treatment Patients on randomised treatment but without a week 52 assessment for other reasons than inability to perform walking test	Impute in own arm based on 'Available on randomised treatment'
	No	**Physically unable to perform walking test and discontinued** Patients who discontinued randomised treatment prematurely, returned to have a week 52 assessment but were unable to perform walking test	Incorporate into endpoint (composite strategy)
		Death Patients without a week 52 assessment due to death	Incorporate into endpoint (composite strategy)
		Missing and discontinued Patients who discontinued randomised treatment prematurely and did not return to have an assessment at week 52.	Impute in own arm based on 'Available but discontinued'

Secondary estimand

The secondary estimand for the primary endpoint (see section 1.1.1), will be based on all randomised patients (full analysis set) and the on-treatment without rescue treatment observation period.

The maximum walking distance will be log-transformed and the change from baseline to the 52 weeks will be analysed using a mixed model for repeated measurements (MMRM). The model will include measurements at both week 26 and 52 as dependent variables. The independent effects included in the model will be treatment and region (Europe, North America and Asia) as categorical fixed effects and baseline maximum walking distance (log-transformed) as a covariate, all nested within visit (week) as a factor. An unstructured covariance matrix for measurements within the same patient will be employed.

From the MMRM model the treatment difference at week 52 will be estimated and the corresponding 95% confidence interval and p-value will be calculated. The estimated treatment difference and confidence intervals will be back transformed to original scale, and thus present the estimated treatment ratio with confidence interval.

5.3.3 Sensitivity analysis

As a sensitivity analysis for the primary estimand, a two-dimensional tipping point analysis will be performed. Missing data will be imputed according to the primary multiple imputation approach and fixed values δ_1 and δ_2 will be added to each imputed value in the semaglutide arm and placebo arm, respectively. The primary analysis will then be performed with these delta-adjusted imputations. This will be repeated for a grid of (δ_1, δ_2)-values, including scenarios where patients

with missing values in the semaglutide arm have worse outcomes than those in the placebo arm. This sensitivity analysis evaluates the robustness of the superiority conclusion to deviations from the MAR assumption for missing data. The tipping point sensitivity analysis will only be performed, if superiority has been confirmed in the primary analysis.

There are no planned sensitivity analyses for the secondary estimand.

5.4 Secondary endpoints analysis

5.4.1 Confirmatory secondary endpoints

As per the hierarchical strategy (section 2) superiority is considered confirmed for a secondary confirmatory endpoint if the p-value is strictly below 0.05 and all previous null hypotheses have been rejected in favour of semaglutide 1 mg.

5.4.1.1 Definition of endpoints

The confirmatory secondary endpoints are:

- Ratio to baseline (week 0) at week 57 in maximum walking distance
- Change from baseline (week 0) to week 52 in VascuQoL-6 score
- Ratio to baseline (week 0) at week 52 in pain-free walking distance

The maximum walking distance at follow-up will be measured in meter or feet and will be handled in the same way as described for the primary endpoint (see section 5.3.1).

The VascuQoL-6 is a PAD-specific questionnaire with 6 items covering social, emotional, functional as well as pain- and symptom-related aspects of the patient´s overall quality of life. The six items evaluate limitation in activities (activity), tiredness in the legs (symptom), walking ability (activity), concerns about poor circulation in the legs (emotional aspects), ability to take part in social activities (social aspects) and discomforts from pain in the leg (pain). Each item has a four-point response scale (where 1 = most problems and 4 = no problems). A summary raw score can be calculated, ranging from 6 to 24 (where higher scores indicate less severe limitation), by summating the score on each question. A higher value indicates better health.

For each patient, imputation of the VascuQol-6 items will be done if at least 50 % of the items have been answered. Missing values for VascuQoL-6 items at a visit will be based on the mean value of all the answered questions of all patients for the item at that particular visit, if the requirement of responses to 50% of the items was satisfied (i.e. assuming 'missing at random').[8]The pain-free walking distance on the treadmill will be measured in meter or feet and will be handled in the same way as described for the primary endpoint (see section 5.3.1).

5.4.1.2 Main analytical approach

Maximum walking distance at follow-up

The analytical approach for the confirmatory secondary endpoint ratio to baseline (week 0) at week 57 in maximum walking distance will be similar to the analytical approach described for the primary endpoint.

Maximum walking distance at follow-up, secondary estimand (confirmatory testing)

Missing data at week 57 will be given an extreme unfavourable rank for patients who died or were physical unable to perform the treadmill test in the same way as described in section 5.3.2. The imputation for patients with missing values for other reasons than death or inability to perform the test will be performed based on the patient's treatment status at week 52, as the week 57 visit is a follow-up visit. The sequential conditional linear regression used to impute monotone missing values, will continue to the last planned visit at week 57.

The confirmatory statistical testing will be based on the p-value from the pooled standardised Wilcoxon test statistic from the 500 multiply imputed data sets.

Maximum walking distance at follow-up, secondary estimand (hypothetical)

The maximum walking distance at week 57 will also be analysed using the MMRM as described for the secondary estimand for the primary endpoint, but the model will include measurements at both week 26, 52 and 57 as dependent variables. As week 57 is a follow-up visit, the patients will not be on the randomised treatment. Thus, the analysis for the follow-up endpoint will be based on the treatment completion status at week 52 without receiving rescue medication.

VascuQol-6

The VascuQoL-6 score will be kept on original scale (will not be log-transformed) for the analyses.

The VascuQoL-6 will be summarised by treatment, and week, both as a total (summated) score and at individual item level. In addition, items will be presented as shift tables, for all non-missing items, as shift from baseline score by treatment and week.

VascuQol-6, secondary estimand (confirmatory testing)

The estimand for confirmatory testing for VascuQoL-6 (Secondary 1, Table 2) is similar to the primary estimand but analysing change in VascuQol-6 score from baseline to week 52.

Specifically, the estimand will be based on all randomised patients (full analysis set) and the in-trial observation period and, as per the composite strategy for handling intercurrent events, missing values for patients who died before week 52, will be handled by ascribing them an extreme unfavourable rank.

The missing values will be ranked in the same way and using the same rules as described for the primary estimand for the primary endpoint, with the only exception that for VascuQoL-6 there will not be any intercurrent events of the type 'patients being physically unable to perform the test' (no. 2). Patients with missing values for the VascuQoL-6 due to other reasons than death will have their values imputed using multiple imputation under a missing at random (MAR) assumption similarly as described for the primary endpoint.

The confirmatory statistical testing will be based on the p-value from the pooled standardised Wilcoxon test statistic from the 500 multiple imputed data sets.

For the estimation of effect, since VascuQol-6 is analysed on an absolute scale, the Hodges-Lehman estimator will reflect the median treatment difference and 95% confidence interval.

VascuQol-6, secondary estimand (hypothetical)

The secondary estimand for VascuQoL-6 (see section 1.1.2, Secondary 2) is similar to the secondary estimand in section 5.3.2 for the primary endpoint, analysing change in VascuQol-6 score from baseline to week 52.

Specifically, it will be based on all randomised patients (full analysis set) and the on-treatment without rescue treatment observation period. The MMRM model will be similar to that in section 5.3.2 but adjusting for baseline VascuQol-6 score as a covariate (not log-transformed).

From the MMRM model the treatment difference at week 52 will be estimated and the corresponding 95% confidence interval and p-value will be calculated.

Pain-free walking distance

The analytical approach for the confirmatory secondary endpoint ratio to baseline (week 0) at week 52 in pain-free walking distance will be similar to the analytical approach described for the primary endpoint.

Pain-free walking distance, secondary estimand (confirmatory testing)

The definition of the estimand for confirmatory testing for pain-free walking distance (Secondary 1, Table 2) is the same as described in section 5.3.2, for the primary estimand, but with 'pain-free walking distance' instead of 'maximum walking distance'.

In particular, confirmatory statistical testing will be based on the p-value from the pooled standardised Wilcoxon test statistic from the 500 multiply imputed data sets.

Pain-free walking distance, secondary estimand (hypothetical)

The definition of the secondary estimand for pain-free walking distance (Secondary 2, Table 2) is the same as the secondary estimand in section 5.3.2 for the primary endpoint, but with 'pain-free walking distance' instead of 'maximum walking distance'.

5.4.1.3 Sensitivity analysis

Two-dimensional tipping point analysis

Sensitivity analysis related to maximum walking distance at follow up, VascuQoL-6 and pain-free walking distance for the secondary estimand used for confirmatory testing, will be a two-dimensional tipping point analysis, as described for the primary endpoint in section 5.3.3.

Handling treadmill assessments >7 weeks between week 52 and week 57

The treadmill assessment for the follow-up visit must be performed at week 57 with a visit window of 7 days from week 52 (end of treatment visit) with a visit window of ±7 days. Following the

confirmatory secondary estimand, the confirmatory statistical analysis will be performed regardless of the time frame window (≤7 weeks) between week 52 and week 57 assessments.

A sensitivity analysis based on the secondary estimand used for confirmatory testing will be performed by considering the assessments of those patients with window > 7 weeks as missing under missing at random (MAR) assumption. The analytical approach for the endpoint ratio to baseline (week 0) at week 57 in maximum walking distance and pain-free walking distance will be similar to the analytical approach described for the primary endpoint.

5.4.2 Supportive secondary endpoints

The supportive secondary endpoints are the following:

- Change from baseline (week 0) to week 57 (follow-up) in pain-free walking distance on a constant load treadmill test
- Change from baseline (week 0) to week 52 in HbA_{1c}
- Change from baseline (week 0) to week 52 in body weight
- Change from baseline (week 0) to week 52 in systolic blood pressure
- Change from baseline (week 0) to week 52 in lipids:
  - total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides
- Change from baseline (week 0) to week 52 in ankle-brachial index (ABI)
- Change from baseline (week 0) to week 52 in toe-brachial index (TBI)
- Change from baseline (week 0) to week 52 in Walking Impairment Questionnaire (WIQ) global score
- Change from baseline (week 0) to week 52 in Short Form 36 (SF-36) physical functioning domain

Follow-up pain free walking distance

The ratio to baseline in pain free walking distance at follow-up will be analysed similarly to the primary endpoint (section 5.3.2).

Ratio to baseline in pain free walking distance at week 57

The pain free walking distance at week 57 will be analysed as described for the primary estimand for the primary endpoint.

Missing data at week 57 will be given an extreme unfavourable rank for patients who died or were physical unable to perform the treadmill test in the same way as described in section 5.3.2. The imputation for patients with missing values for other reasons than death or inability to perform the test will be performed based on the patient's treatment status at week 52, as the week 57 visit is a follow-up visit. The sequential conditional linear regression used to impute monotone missing values, will continue to the last planned visit at week 57.

The treadmill tests at week 57 will also be analysed using the MMRM as described for the secondary estimand for the primary endpoint, but the model will include measurements at both week 26, 52 and 57 as dependent variables. As discussed in the secondary estimand (hypothetical) for maximum walking distance at follow-up visit, the analysis for the pain-free walking distance at

week 57 will be based on the treatment completion status of the patient at week 52 without receiving rescue medication.

HbA_{1c}, body weight, and systolic blood pressure

The analyses of change in HbA_{1c}, body weight and systolic blood pressure will be based on all randomised patients (full analysis set) and the on-treatment without rescue treatment observation period.

The systolic blood pressure will be measured as the mean of the last and the second last measurement at the given visit.

The change from baseline to week 52 will be analysed using a MMRM, with treatment and region (Europe, North America and Asia) as a factors, and baseline value as a covariate, all nested within visit (week) as a factor. All post-baseline measurements in the on-treatment without rescue treatment period will be included as dependent variables. An unstructured covariance matrix for measurements within the same patient will be employed.

From the MMRM model the treatment difference at week 52 will be estimated and the corresponding 95% confidence interval and p-value will be calculated.

ABI and TBI

The analyses of ABI and TBI will be based on all randomised patients (full analysis set) and the on-treatment without rescue treatment observation period.

The ABI and TBI will be measured at both right and left leg for each patient. The overall ABI and TBI at the baseline, week 26 and 52 for each patient will be defined as the lower of the left and right ABI and TBI, respectively.

The ABI and TBI will be log-transformed and the change from baseline to week 52 will be analysed using a MMRM. All post-baseline measurements in the on-treatment without rescue treatment period will be included as dependent variables. The independent effects included in the model will be treatment and region as categorical fixed effects and baseline value (log-transformed) as a covariate, all nested within visit (week) as a factor. An unstructured covariance matrix for measurements within the same patient will be employed.

From the MMRM model the treatment difference at week 52 will be estimated and the corresponding 95% confidence interval and p-value will be calculated. The estimated treatment difference and confidence intervals will be back transformed to original scale, and thus present the estimated treatment ratio with confidence interval.

Lipids

The analyses of the lipids will be based on all randomised patients (full analysis set) and the on-treatment without rescue treatment observation period.

The lipids will be measured as total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides, and analysed separately.

The lipids will be log-transformed and the change from baseline to week 52 will be analysed using a MMRM. The model will include measurements at both week 12 and 52 as dependent variables. The independent effects included in the model will be treatment and region as categorical fixed effects and baseline lipid (log-transformed) as a covariate, all nested within visit (week) as a factor. An unstructured covariance matrix for measurements within the same patient will be employed.

From the MMRM model the treatment difference at week 52 will be estimated and the corresponding 95% confidence interval and p-value will be calculated. The estimated treatment difference and confidence intervals will be back transformed to original scale, and thus present the estimated treatment ratio with confidence interval.

Walking Impairment Questionnaire (WIQ) global score

The walking impairment questionnaire consists of three domains, speed, distance, and stairclimbing, consisting of in total 14 questions. Each response is weighted based on the difficulty of the task (e.g., the weight for "walk slowly" is 1.5 whereas for the weight for "run or jog" is 5). Domain scores are determined by dividing the weighted answers by the maximum possible weighted score and multiplying by 100. In each domain the score can range from 0 to 100% with lower scores indicating lower performance. An overall (global) score is calculated as the mean of the three domain scores. The questionnaire also consists of questions related to PAD, but these questions are not part of the overall score.

When items are missing for the WIQ, the questions with missing responses are removed from the denominator of the weighted score to calculate a percent score based on the items that remains.[9] At least 50 % of the questions have to be answered, for a subscale score to be calculated, and at least two of the three domains needs a result for the overall WIQ score to be calculated. In addition, a best and worst case scenario will be made for all missing responses. The best and worst case scenarios are created by taking the answered questions into account, and assuming that patients could never score higher on a harder task and never lower on an easier task.[8] The best case considers a hypothetical scenario, where the patient experiences no difficulty in walking and rates the best score ('4') on all the missing items in a domain. On the other hand, the worst case scenario envisages a scenario, where the patient experiences extreme difficulty in walking and hence assigns the worst score ('0') for all missing items in a domain. The details regarding best- and worst-case scenario can be found in Appendix 3.

The WIQ questionnaire will be summarised by domains and total score by treatment and visit.

The analyses of change in total WIQ will be based on all randomised patients (full analysis set) and the on-treatment without rescue treatment observation period, and a MMRM model as described for e.g. HbA_{1c} will be used. Analyses will be repeated on best and worst case scenarios.

SF-36 physical functioning domain

The SF-36 physical functioning domain will be based on the SF-36v2 (acute version) with a 1-week recall period containing 36 items.

A total of 35 items measure eight domains of functional health and well -being: physical functioning (10 items), role limitation due to physical health problems (4 items), bodily pain (2

items), general health perceptions (5 items), vitality (4 items), social functioning (2 items), role limitations due to emotional problems (3 items) and general mental health (5 items). There is an additional single item giving information on health change over the past week. The information obtained on the eight domains of health will be further aggregated into two summary component measures of physical and mental health (PCS, MCS).

The domain scores will be norm-based scores derived using the Optum's PRO CoRE software. Missing data will be handled using the Maximum Data Recovery method. The Software applies a value to a domain item rendered missing if at least one of the items in that domain has valid data. A domain receives a "missing" score (".") only if all the items in that domain are missing. PCS and MCS will be calculated when at least seven of the eight profile domains have valid data, either actual or estimated. However, to calculate PCS, the physical functioning domain must be one of the seven domains having valid data. Also, to calculate MCS, the mental health domain must be one of the seven domains having valid data.

The SF-36 will be summarised by domains and component summary scores by treatment and visit.

The analyses of change in physical functioning will be based on all randomised patients (full analysis set) and the on-treatment without rescue treatment observation period, and a MMRM model as described for e.g. HbA_{1c} will be used.

5.5 Exploratory endpoints analysis

The exploratory endpoint is the following:

- Change from baseline (week 0) to week 52 in mean daily number of steps

Mean daily number of steps

The daily number of steps will be based on measurements from a physical activity tracker. The activity tracker is the ActiGraph device, and step counts will be based on the ActiGraph step count algorithm.[10]

The activity tracker is applied in a subset of 125 patients. The activity tracker will be wrist-worn, and the daily activity level will be measured in a 2-week period in the beginning of the trial, and in the end.

The mean daily number of steps will be a mean of the daily step counts during the 2-week period up to the baseline visit as baseline value and up to week 52 (week 51 and 52) as the week 52 value. All physical activity data is used, and no imputations of data are done in case data are missing due to non-wear. The mean number of steps will not be adjusted for non-wear time.

The analysis of mean daily number of steps will be based on the subset of all randomised patients (subset of full analysis set) and the on-treatment without rescue treatment observation period.

The change from baseline to week 52 in mean number of steps will be analysed using an analysis of covariance (ANCOVA) model, with treatment and region as factors, and baseline mean number of steps as a covariate.

From the ANCOVA model the treatment difference at week 52 will be estimated and the corresponding 95% confidence interval and p-value will be calculated.

5.6 Safety analyses

Safety is a secondary objective in the trial. All safety analyses will be made on the safety analysis set.

5.6.1 Extent of exposure

Number of days in treatment period and number of days exposed to trial product will be summarised by treatment group. The treatment period will be defined as the period from first drug date of first dose of trial product until date of last dose on trial product, both days included. The number of days exposed to trial product will be the treatment period subtracted any days in the period with temporary treatment discontinuation (as recorded in the CRF). Number of days exposed to trial product will also be summarised by dose and subgroups (age, gender and region)

5.6.2 Adverse events

The following adverse events will be collected in the trial:

- Serious Adverse Events (SAEs)
- AEs leading to discontinuation of trial product
- Pregnancies
- Episodes of severe hypoglycaemia
- Selected types of Adverse Events (SAEs and non-SAEs) requiring additional data collection and events for adjudication (See Table 10).
- Technical complaints

Pregnancies and Technical complains will only be listed.

All Adverse Events (AEs) will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). A Treatment Emergent Adverse Event (TEAE) is defined as an AE with onset in the on-treatment observation period (see definition of observation periods in section 4).

An independent external event adjudication committee (EAC) will perform blinded adjudication of the selected AEs, as listed in Table 10. The adjudicated events will be defined based on outcomes of the EAC evaluations. Selected AEs requiring additional data collection is also listen in Table 10.

Table 10 List of selected types of AEs

	Type of AE
Event for adjudication	• Death • Acute coronary syndrome • Stroke or transient ischemic attach • Acute or chronic limb ischemia requiring hospitalisation
Requiring additional data collection	• Events leading to coronary artery revascularisation (ACS and non-ACS) • Events leading to carotid artery revascularisation • Events leading to peripheral artery revascularisation • Medication error • Misuse and abuse

The TEAEs in the categories 'Serious Adverse Events (SAEs)', 'AEs leading to discontinuation of trial product' and 'Selected Adverse Events' will be summarised by treatment and by system organ class, preferred term, severity, outcome and relation to trial product. The TEAEs are summarised descriptively in terms of the number of patients with at least one event (N), the percentage of patients with at least one event (%), the number of events (E) and the event rate per 100 years (R). The SAEs will also be summarized by subgroups: regions (Europe, North America and Asia), age groups (<65, ≥ 65 years) and sex (Male, Female). Non-treatment emergent AEs will be presented in listings. Fatal SAEs will be presented in a separate listing.

Severe hypoglycaemic episodes

Severe hypoglycaemic episodes will be defined as treatment-emergent if the onset of the episode occurs within the on-treatment observation period (see definition of observation periods in Section 4).

Treatment-emergent severe hypoglycaemic episodes will be presented in terms of the number of patients with at least one episode, the percentage of patients with at least one episode (%), the total number of episodes and the episode rate per 100 patient years of exposure time.

The number of treatment-emergent severe hypoglycaemic episodes will be analysed using a negative binomial regression model with a log-link function and the logarithm of the duration of the patients on-treatment observation period as offset. The model will include treatment as factor and baseline HbA_{1c} as covariate. The estimated rate ratio between semaglutide 1 mg and placebo will be presented together with the 95% CI and p-value.

If only fewer number of events are observed in either of treatment arms or no events are observed in any of the arms, the statistical analysis will not be performed, and the data will only be summarised.

Non-treatment emergent severe hypoglycaemic episodes will be presented in listings.

5.6.3 Additional safety assessments

Additional safety assessments in the trial are:

- Physical examination, pulse rate and diastolic blood pressure
- Eye examination
- Laboratory assessments (see Table 11)

The additional safety assessments will be summarised descriptively by treatment group and visit. Categorical safety endpoints will be summarised as counts and relative frequencies.

Table 11 Safety laboratory assessments

Haematology	Biochemistry
• Erythrocytes • Haematocrit • Haemoglobin • Leucocytes • Thrombocytes	• Albumin • Creatinine • Potassium • Sodium

5.7 Other analyses

5.7.1 Exploratory analyses of treadmill test

Median treatment difference of the ratio to baseline in treadmill test

In the analyses described in Section 5.3.2 and 5.4.1.2 the Hodges-Lehmann estimator gave the median treatment ratio of the ratio to baseline in treadmill tests and 95% confidence intervals. To obtain an estimate of the median treatment difference in the ratio to baseline at week 52 in maximum walking distance and pain-free walking distance, the Hodges-Lehmann estimator will be applied in a similar manner on ratio to baseline data (back transformed from the log-transformed observed or imputed data). Results after application of Rubin's rule will show the median treatment difference of the ratio to baseline at week 52 and 95% confidence intervals.

Change from baseline in treadmill test at week 52

In order to get an estimate of the treatment difference in the treadmill test in meters, the analyses described for the primary and secondary estimand for the primary endpoint, will be made for change from baseline in maximum walking distance and pain-free walking distance at week 52 (instead of ratio to baseline).

The change from baseline in maximum walking distance and pain free walking distance at week 52 will be analysed similarly to the primary endpoint (section 5.3.2), but the analyses will be based on original data (not log-transformed).

The Hodges Lehmann estimator after multiple imputation will show the median treatment difference and 95% confidence interval.

From the MMRM model (the secondary estimand) the treatment difference at week 52 will be estimated and the corresponding 95% confidence interval will be calculated.

5.7.2 Estimate of meaningful within-patient change (MWPC)

Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) items will be used for anchor-based analyses as primary and supportive anchor respectively to determine meaningful within-patient change for the maximum walking distance and the VascuQoL-6 summary score. In addition, distribution-based responsiveness will be assessed for both maximum walking distance and VascuQoL-6 total score to support results from the anchor-based method.

Anchor-based method

The anchor will be based on change from baseline to week 52 in global impression of severity scale (PGI-S). The global impression of change scale (PGI-C) at week 52 will only be a supportive measure due to the long recall period. The item and response options for the PGI-S and PGI-C are described below (Table 12). Both scales are simple, direct, easy-to-use scales that are intuitively understandable to patients and clinicians and the ratings can be clearly associated with the primary objective of walking ability.

Table 12 PGI-S and PGI-C categories related to walking ability

PGI-S scale	PGI-C scale
How would you rate your current limitation in walking ability?	Please choose the response below that best describes the overall change in your walking ability since you started taking the trial medication.
1. None 2. Mild 3. Moderate 4. Severe	1. Much better 2. A little better 3. No change 4. A little worse 5. Much worse

The change in PGI-S can range from an increase of 3 (+3) to a decrease of 3 (-3). The change in PGI-S will be categorised as: 'Decrease >=2', 'Decrease=1', 'No change', 'Increase=1' and 'Increase>=2', with the category 'Decrease >=2' being the best outcome (e.g. rating the limitation in walking ability as Severe (4) at baseline and Mild (2) at week 52), and 'Increase >=2' being the worst outcome.

The PGI-S and PGI-C will be handled as specified in Table 13 in case of missing data for the treadmill test or intercurrent events.

Table 13 Handling of PGI-S and PGI-C in case of missing data or intercurrent events

Scenario	PGI-S	PGI-C
Patients who died	Increase>=2	Much worse
Patients who are unable to perform the treadmill test	As rated by the patient. If missing: Increase>=2	As rated by the patient. If missing: 'Much worse'
Missing treadmill test for other reasons	As rated by the patient. If missing: No imputation, assuming missing at random	As rated by the patient. If missing: No imputation, assuming missing at random

Missing data for PGI-S or PGI-C, where the treadmill test data are available, will be considered missing at random, and kept missing.

Descriptive statistics, cumulative distribution functions and probability functions will be used to evaluate the association between the anchor and the primary endpoint, as described in *Discussion Document for Patient-Focused Drug Development Public Workshop.*[11]

The ratio to baseline at week 52 in maximum walking distance will be summarised for all patients (not split by treatment group) by Change in PGI-S category and by PGI-C category as N (total number), geometric mean, %CV, median, IQR, 5^{th} and 95^{th} percentile. Boxplots by change in PGI-S category and PGI-C category will also be prepared. For each of the change in PGI-S categories the ratio to baseline at week 52 in maximum walking distance will be summarised by PGI-S at week 52 as N (total number) and 10^{th}, 25^{th}, 50^{th}, 75^{th} ,90^{th} percentiles and IQR. E.g. for the PGI-S category 'Decrease=1' the percentiles of ratio to baseline at week 52 in maximum walking distance will be shown by PGI-S at week 52 categories 'None', 'Mild' and 'Moderate', where the following transitions can be observed: Severe → Moderate; Moderate → Mild; Mild → None.

A meaningful change for the patient will be determined based on the PGI-S as:

- PGI-S: A 1-category decrease on the 4-category scale (Category 'Decrease=1')

A threshold for meaningful within-patient change in maximum walking distance will be established as the median ratio to baseline at week 52 in maximum walking distance for the patients fulfilling the PGI-S criteria as defined above.

Cumulative distribution function (CDF) curves of the ratio to baseline at week 52 in maximum walking distance will be presented by the change in PGI-S categories: 'Decrease >=2', 'Decrease=1', 'No change', 'Increase=1' and 'Increase>=2'. CDFs present a continuous plot of the proportion of patients with a ratio to baseline at week 52 in maximum walking distance at or above a given value.

The probability density function (PDF) curves of the ratio to baseline at week 52 in maximum walking distance will be estimated using the kernel density estimator and presented for the same PGI-S categories.

Likewise, the CDF and PDF will be presented by the five PGI-C categories.

To evaluate whether the treatment effect is in the range that patients consider to be clinically meaningful, the CDF curves of the ratio to baseline at week 52 in maximum walking distance will be presented by the treatment groups.

The change from baseline at week 52 in maximum walking distance (meters) will be summarised for all patients (not split by treatment group) by Change in PGI-S category and by PGI-C category as N (total number), mean, standard deviation, median, IQR, 5^{th} and 95^{th} percentiles, minimum/maximum. The CDF and PDF curves described above will also be presented based on change from baseline at week 52 in maximum walking distance (meters).

Distribution based method

An estimate of the within-patient standard deviation will be made using the average of two baseline measurements of maximum walking distance (treadmill test). The SD used for calculation of 0.5*SD is a combination of measurement variation and variation of the study population. There is no linkage between this, and the magnitude of change needed to be clinically relevant (from a patient, clinician or other perspective). The 0.5*SD is included for information only, since it traditionally has been used as a responder threshold in many contexts.

Meaningful within-patient change in VascuQol-6 total score

The VascuQol-6 measures symptoms and functional impairment for patients with T2D and PAD. A meaningful change for the patients in VascuQol-6 will be estimated in the same way as the anchor-based method described for the maximum walking distance. Hence, a meaningful change in VascuQol-6 for the patient will be determined based on the PGI-S as:

PGI-S: A 1-category decrease on the 4-category scale (Category 'Decrease=1')

The PGI-S and PGI-C items and response options are presented below (see Table 14).

Table 14 PGI-S and PGI-C categories related to symptoms and impact on quality of life

PGI-S scale	PGI-C scale
How would you rate the impact of poor circulation in your legs on your current quality of life?	Thinking about the poor circulation in your legs, how has your quality of life changed since you started the study medication?
1. No impact 2. Mild impact 3. Moderate impact 4. Severe impact	1. Much improved 2. A little improved 3. No change 4. A little worsened 5. Much worsened

The threshold for meaningful within-patient change for the VascuQol-6 will be established as the median difference in the VascuQol-6 change score for patients fulfilling a 1-category improvement on the PGI-S.

Correlations between change in the VascuQol-6 total score and change in the PGI-S will provide support for the use of the PGI-S as an anchor. These correlations should be no smaller than the recommended correlation of 0.371 between PRO change and the anchor measure[12] or certainly exceed the minimum correlation of 0.30 advocated in more recent literature[13].

The PGI-S and PGI-C will be handled as specified in Table 12 in case of missing data for the VascuQoL-6 or intercurrent events, except that for intercurrent events of 'Patients who died' the PGI-C category will be 'Much worsened' and there will not be any intercurrent events of 'Patients who are unable to perform the treadmill test'.

The change from baseline at week 52 in VascuQoL-6 total score will be summarised for all patients (not split by treatment group) by Change in PGI-S category and by PGI-C category as N (total number), mean, standard deviation, median, IQR, 5th and 95th percentiles and minimum/maximum. The change from baseline for individual items will be summarised in the same way. All other summary statistics, CDF curves, PDF curves and distribution-based method will be presented for the VascuQoL-6 total score, in the same way as described for the maximum walking distance.

Responder analysis based on MWPC thresholds

If superiority of the clinical outcome assessments – maximum walking distance and VascuQoL-6 total score at week 52 is confirmed, then the clinical relevance of the treatment effect is assessed by a responder analysis based on the proportions of patients in each treatment group who have experienced a clinically relevant improvement in symptoms and function as measured by the respective endpoints.

Analysis addressing the primary estimand

To account for missing data, the binary endpoints will be derived from the 500 imputed datasets described in section 5.3.2. Each of the complete data sets will be analysed using a logistic regression model with treatment as fixed effects and associated baseline response as covariate. Estimated odds ratios (OR) will be log transformed and inference will be drawn using Rubin's rule. The results will be back-transformed and described by the odds ratio between treatments and the associated 95% CI and p-value for no treatment difference.

In addition to the estimated OR, the estimated treatment differences will be provided by calculating the responder probabilities and treatment differences between responder probabilities based on the logistic regression model, with confidence intervals for treatment differences obtained using the delta method.

5.7.3 Subgroup analyses

To assess consistency of treatment effect for maximum walking distance at week 52 across regions (Europe, North America and Asia), age groups (<65, ≥ 65 years) and sex (Male, Female), a subgroup analyses will be performed.

The analysis will be based on the secondary estimand for the primary endpoint (the hypothetical estimand), and on all randomised patients (full analysis set) and the on-treatment without rescue treatment observation period.

The treatment by subgroup interaction will be added to the MMRM model specified in Section 5.3.2 (secondary estimand for the primary endpoint). The model will include measurements at both week 26 and 52 as dependent variables. The independent effects included in the model will be treatment, region, subgroup and treatment by subgroup as categorical fixed effects and baseline maximum walking distance (log-transformed) as a covariate, all nested within visit (week) as a factor. An unstructured covariance matrix for measurements within the same patient will be employed.

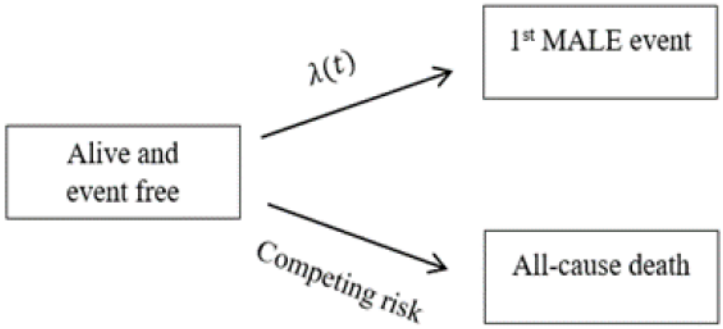
From the MMRM model the treatment difference at week 52 by subgroup will be estimated and the corresponding 95% confidence interval. The estimated treatment differences and confidence intervals will be back transformed to original scale, and thus present the estimated treatment ratio with confidence interval. The estimated treatment ratio with confidence interval by subgroup will be displayed in a forest plot.

Level of significance for treatment by subgroup interaction will be 5%.

5.7.4 Time to first occurrence of major adverse limb events (MALE)

The time to first occurrence of MALE (acute limb or chronic limb ischemia hospitalisation) will be analysed using the Cox proportional hazards model with treatment group as a fixed factor under the assumption of independent censoring. The statistical analysis will be based on the FAS and in-trial observation period. The hazard ratios (HR) together with 95% confidence interval and two-sided p values will be reported from the model.

For MALE, all-cause death is a competing risk terminating the observation for the event of interest. The figure given below illustrates competing risk as a multi-state model for MALE, where $\lambda(t)$ is the hazard rate of interest and t being time since randomisation.



Terminated observations (due to competing risks) are technically treated as censored observations but are not part of the independent censoring assumption. The population-level summary measure is the HR for semaglutide 1.0 mg versus placebo. Tied event times are handled using the exact method and confidence intervals are based on the profile likelihood.

Cumulative incidence functions for the MALE are estimated by the Aalen-Johansen estimator which accounts for competing risks.

5.8 Interim analyses

Not applicable

5.8.1 Data monitoring committee

Not applicable

6 Supporting documentation

6.1 Appendix 1 List of abbreviations

AE	adverse event
ABI	Ankle-brachial index
ANCOVA	Analysis of Covariance
CDF	cumulative distribution function
CI	confidence interval
CV	Coefficient of variation
EAC	Event adjudication committee
EM	Expectation-Maximization
ETR	Estimated treatment ratio
HR	Hazard ratio
IQR	Interquartile range
LLOQ	Lower Limit of Quantification
MALE	Major adverse limb events
MAR	Missing at random
MedDRA	medical dictionary for regulatory activities
MCS	Mental component summary
MMRM	mixed model for repeated measurements
MWPC	meaningful within-patient change
PCS	Physical component summary
PDF	probability density function
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
OR	Odds ratio
SAP	Statistical Analysis Plan

SF-36	Short Form 36
std	Standard deviation
TEAS	Treatment Emergent Adverse Events
TBI	Toe-brachial index
TFL	Tables, figures and listings
WIQ	Walking Impairment Questionnaire

6.2 Appendix 2: Changes to protocol-planned analyses

- **Sensitivity Analysis – Handling treadmill assessments >7 weeks between week 52 and week 57:** To ensure the follow-up treadmill assessment is carried out within the window of ≤ 7 weeks from the end of treatment visit (week 52). If the patient has carried out the follow-up assessment after a window of 7 weeks, then that observation would be treated as missing as that would not necessarily reflect the true sustained effect of the treatment on the endpoint considering the half-life of Semaglutide 1.0 mg.

- **Additional subgroups by age groups and sex:** The consistency of treatment effect for maximum walking distance at week 52 will be evaluated by a subgroup analysis based on the hypothetical estimand for region, age groups and sex. Additionally, the serious adverse events will be summarised by these groups.

- **ABI and TBI analysis – Ratio to baseline at week 52:** The endpoints will be first log-transformed and the analysis will be carried out using the MMRM model based on the hypothetical estimand. The estimates will be back transformed from log scale, thus presenting the estimated treatment ratio [ETR] along with its 95% CI.

- **Responder analysis for both maximum walking distance and VascuQoL-6 total score based on meaningful-within patient change (MWPC) thresholds:** Once superiority of the endpoints is achieved, the clinical relevance of the treatment effect will be evaluated by performing a responder analysis based on the thresholds for MWPC obtained from the anchor-based method for the primary anchor (PGI-S) category.

- **Analysis on time to first occurrence of major adverse limb events [MALE]:** Exploratory analysis is carried out to evaluate the effect of Semaglutide 1.0 mg in reducing the incidence of MALE events.

- **WIQ total score – best & worst-case scenarios:** To describe the derivation of best- & worst-case total scores for WIQ in the presence of missing items and to perform the statistical analysis for the both the scenarios.

6.3 Appendix 3: Definition and calculation of endpoints, assessments and derivations

6.3.1 Endpoint derivations and assessments

Type	Title	Time frame	Unit	Details
Primary endpoint	Change in maximum walking distance on a constant load treadmill test	From baseline (week 0) to week 52	Ratio to baseline (no unit)	Converted to meters and log transformed
Confirmatory secondary endpoint	Follow-up change in maximum walking distance on a constant load treadmill test	From baseline (week 0) to week 57	Ratio to baseline (no unit)	Converted to meters and log transformed
Confirmatory secondary endpoint	Change in Vascular Quality of Life Questionnaire-6 (VascuQoL-6) score	From baseline (week 0) to week 52	Score (no unit, range: 6 to 24)	
Confirmatory secondary endpoint	Change in pain-free walking distance on a constant load treadmill test	From baseline (week 0) to week 52	Ratio to baseline (no unit)	Converted to meters and log transformed
Supportive secondary endpoint	Follow-up change in pain-free walking distance on a constant load treadmill test	From baseline (week 0) to week 57	Ratio to baseline (no unit)	Converted to meters and log transformed
Supportive secondary endpoint	Change in HbA_{1c}	From baseline (week 0) to week 52	%-point	
Supportive secondary endpoint	Change in body weight	From baseline (week 0) to week 52	Kilogram	
Supportive secondary endpoint	Change in systolic blood pressure	From baseline (week 0) to week 52	mmHg	
Supportive secondary endpoint	Change in total cholesterol	From baseline (week 0) to week 52	Ratio to baseline (no unit)	
Supportive secondary endpoint	Change in LDL-cholesterol	From baseline (week 0) to week 52	Ratio to baseline (no unit)	
Supportive secondary endpoint	Change in HDL-cholesterol	From baseline (week 0) to week 52	Ratio to baseline (no unit)	
Supportive secondary endpoint	Change in triglycerides	From baseline (week 0) to week 52	Ratio to baseline (no unit)	
Supportive secondary endpoint	Change in ankle-brachial index (ABI)	From baseline (week 0) to week 52	Ratio (no unit)	

Type	Title	Time frame	Unit	Details
Supportive secondary endpoint	Change in toe-brachial index (TBI)	From baseline (week 0) to week 52	Ratio (no unit)	
Supportive secondary endpoint	Change in Walking Impairment Questionnaire (WIQ) global score	From baseline (week 0) to week 52	%-point	
Supportive secondary endpoint	Change in Short Form 36 (SF-36) physical functioning domain	From baseline (week 0) to week 52	Score, no unit (range: 19.03 to 57.60)	
Exploratory endpoint	Change in mean daily number of steps	From baseline (week 0) to week 52	Steps	
Assessment	Number of Serious TEAS	From baseline (week 0) to week 52		
Assessment	Number of severe hypoglycaemic episodes	From baseline (week 0) to week 52		
Assessment	Change in PGI-S walking ability	From baseline (week 0) to week 52	Score, no unit (range -3 to 3)	Will also be categorised as (score): 'Decrease >=2'(-3,-2) 'Decrease=1' (-1) 'No change' (0) 'Increase=1' (1) 'Increase>=2' (2, 3)
Assessment	PGI-C walking ability	At week 52	Score, no unit (range 1 to 5)	Categories (score): Much better (1) A little better (2) No change (3) A little worse (4) Much worse (5)
Assessment	Change in PGI-S quality of life	From baseline (week 0) to week 52	Score, no unit (range -3 to 3)	Will also be categorised as (score): 'Decrease >=2'(-3,-2) 'Decrease=1' (-1) 'No change' (0) 'Increase=1' (1) 'Increase>=2' (2, 3)
Assessment	PGI-C quality of life	At week 52	Score, no unit (range 1 to 5)	Categories (score): Much improved (1) A little improved (2) No change (3) A little worsened (4) Much worsened (5)
Assessment	Change in Erythrocytes	From baseline (week 0) to week 52	10^{12}/L	
Assessment	Change in Haematocrit	From baseline (week 0) to week 52	%	

Type	Title	Time frame	Unit	Details
Assessment	Change in Haemoglobin	From baseline (week 0) to week 52	mmol/L	
Assessment	Change in Leucocytes	From baseline (week 0) to week 52	10^9/L	
Assessment	Change in Thrombocytes	From baseline (week 0) to week 52	10^9/L	
Assessment	Change in Albumin	From baseline (week 0) to week 52	g/dL	
Assessment	Change in Creatinine	From baseline (week 0) to week 52	µmol/L	
Assessment	Change in Potassium	From baseline (week 0) to week 52	mmol/L	
Assessment	Change in Sodium	From baseline (week 0) to week 52	mmol/L	
Assessment	Change in pulse rate	From baseline (week 0) to week 52	Beats/min	
Assessment	Change in diastolic blood pressure	From baseline (week 0) to week 52	mmHg	

6.3.2 Derivation of best- and worst- case scenarios for missing items in Walking Impairment Questionnaire (WIQ)

WIQ total score for a domain in case of missing items:

Suppose that $\boldsymbol{\delta}: 0 \leq \delta_{ijk} \leq 100 \in \mathbb{R}$ denotes the total score for the i^{th} patient at the j^{th}scheduled visit for the k^{th}domain of WIQ. The k^{th} domain has $\{1,2,\ldots\ldots,m\}$ items in total and let $n(k)$ denotes the number of items filled in the k^{th} domain, where $\left\lceil\frac{m}{2}\right\rceil \leq n(k) \leq m$.

$$\delta_{ijk} = 100 \times \frac{\sum_{m=1}^{n(k)} w_m x_m}{\sum_{m=1}^{n(k)} w_m x_{best}}$$

This expression denotes the total score for a patient i, at a visit j for the k^{th}domain comprising of $n(k)$ items which has responses recorded. Let w_m be the weight assigned to the m^{th} filled item in the k^{th} domain. Let $0 \leq x_m \leq 4, x_m \in \mathbb{W}$ denote the response scored by the patient for m^{th} item.

Let $x_{best} = max\{\boldsymbol{x}\}$ denote the most favourable outcome that can be reported by a patient (Score: 4). Let $x_{worst} = min\{\boldsymbol{x}\}$ denote the most unfavourable outcome (extreme difficulty) that can be reported by a patient (Score: 0). This is employed for handling missing items at each subscale level to calculate the total score, if atleast 50% of the items for that subscale is filled in.

WIQ best-case total score:

The best-case envisages a hypothetical scenario where the patient scores the best outcome (Score: 4) for all the missing items in a subscale.

$$\delta_{best_{ijk}} = 100 \times \frac{\sum_{m=1}^{n(k)} w_m x_m + \sum_{z=1}^{m-n(k)} w_z x_{best}}{\sum_{r=1}^{m} w_r x_{best}}$$

If δ_{best} is an upper bound of $\boldsymbol{\delta}$ such that $\delta_{best} \leq \delta'_{best}$ for every upper bound δ'_{best}, then δ_{best} is defined as the least upper bound (*Supremum*) of $\boldsymbol{\delta}$. The best outcomes are assigned to $m - n(k)$ missing items in the numerator weighted by their corresponding weights reflecting the total score for the k^{th} domain, had the patient experienced higher perceived walking-performance. Now that the missing items are filled with the best outcomes, we have all the responses available $[n(k) \cup m - n(k)]$, hence the denominator calculations will be based on all the m items in the k^{th} domain similar to the case where the patient has actually filled all the items.

WIQ worst-case total score:

The worst-case envisages a hypothetical scenario where the patient scores the worst outcome (Score:0) for all the missing items in a subscale.

$$\delta_{worst_{ijk}} = 100 \times \frac{\sum_{m=1}^{n(k)} w_m x_m + \sum_{z=1}^{m-n(k)} w_z x_{worst}}{\sum_{r=1}^{m} w_r x_{best}}$$

If δ_{worst} is a lower bound of δ such that $\delta_{worst} \geq \delta'_{worst}$ for every lower bound δ'_{worst}, then δ_{worst} is defined as the greatest lower bound (*Infimum*) of δ. The worst outcomes are assigned to the $m - n(k)$ missing items in the numerator weighted by their corresponding weights reflecting the total score for the k^{th} domain, had the patient experienced lower perceived walking-performance. Now that the missing items are filled with the worst outcomes, we have all the responses available $[n(k) \cup m - n(k)]$, hence the denominator calculations will be based on all the m items in the k^{th} domain like the case where the patient has actually filled all the items.

Furthermore, the best- and worst-case totals will be calculated for each subscale only if 50% of the items in that subscale is filled in. The rules for calculating WIQ global score for the best- and worst-case scenario will be the same as described for WIQ global score.

7 References

1. Regensteiner J, Steiner J, Panzer R, Hiatt W. Evaluation of walking impairment by questionnaire in patients with peripheral arterial disease. *Clinical Research*. 1990;38.2: A515. Web.
2. Nicolaï SP, Kruidenier LM, Rouwet EV, Graffius K, Prins MH, Teijink JA. The walking impairment questionnaire: an effective tool to assess the effect of treatment in patients with intermittent claudication. J Vasc Surg. 2009;50(1):89-94.
3. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
4. Beebe HG, Dawson DL, Cutler BS, Herd JA, Strandness DE, Bortey EB, et al. A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. Arch Intern Med. 1999;159(17):2041-50.
5. Dawson DL, Cutler BS, Hiatt WR, Hobson RW, Martin JD, Bortey EB, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med. 2000;109(7):523-30.
6. Dawson DL, Cutler BS, Meissner MH, Strandness DE. Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double-blind trial. Circulation. 1998;98(7):678-86.
7. Nordanstig J, Pettersson M, Morgan M, Falkenberg M, Kumlien C. Assessment of Minimum Important Difference and Substantial Clinical Benefit with the Vascular Quality of Life Questionnaire-6 when Evaluating Revascularisation Procedures in Peripheral Arterial Disease. Eur J Vasc Endovasc Surg. 2017;54(3):340-7.
8. Conijn A, Jonkers W, Rouwet E, Vahl A, Reekers J, Koelemay M. Introducing the Concept of the Minimally Important Difference to Determine a Clinically Relevant Change on Patient-Reported Outcome Measures in Patients with Intermittent Claudication. Cardiovasc Intervent Radiol. 2015;38:1112-8.
9. Sagar SP, Brown PM, Zelt DT, Pickett WL, Tranmer JE. Further clinical validation of the walking impairment questionnaire for classification of walking performance in patients with peripheral artery disease. Int J Vasc Med. 2012;2012:190641.
10. Bagui S, Fang X, Bagui S, Wyatt J, Houghton P, Nguyen J, et al. An improved step counting algorithm using classification and double autocorrelation. International Journal of Computers and Applications. 2020;1.
11. U. S. Food and Drug Administration. Discussion Document for Patient-Focused Drug Development Public Workshop on Guidance 4: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making. December 6, 2019.
12. Hays RD, Farivar SS, Liu H. Approaches and recommendations for estimating minimally important differences for health-related quality of life measures. COPD. 2005;2(1):63-7.
13. Revicki DA, Hays RD, Cella D, Sloan JA. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol. 2008;61:102-9.