Clinical trial results:
Investigation of clinical comparability of semaglutide drug products based on the proposed and the approved drug substance manufacturing processes in participants with type 2 diabetes

Summary

EudraCT number	2021-001501-69
Trial protocol	SK
Global end of trial date	18 September 2023

Results information

Result version number	v1 (current)
This version publication date	02 October 2024
First version publication date	02 October 2024

Trial information

Trial identification

Sponsor protocol code	NN9535-4820

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05478252
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Alle, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish clinical comparability between semaglutide J subcutaneous (s.c.) and semaglutide B s.c. on change from baseline in HbA1c at week 28 in subjects with T2D as add-on to stable dose of metformin.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, last amended by the 64th World Medical Association General Assembly, October 2013, and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, including archiving of essential documents, E6(R2), Current step 4 version, 09 November 2016 and 21 CFR 312.120.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 August 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	Poland: 84
Country: Number of subjects enrolled	Slovakia: 65
Country: Number of subjects enrolled	United States: 135
Country: Number of subjects enrolled	South Africa: 74
Worldwide total number of subjects	388
EEA total number of subjects	149

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	387
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 73 sites in Slovakia, Poland, South Africa, the United States and Canada.

Pre-assignment

Screening details:

Subjects were randomised in a 3:1 manner to receive either semaglutide J or semaglutide B.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide J

Arm description:

Subjects initially received 0.25 milligrams (mg) subcutaneous injections of semaglutide J once weekly and the dose was then escalated (0.25 mg in week 0 to week 4 and 0.5 mg in week 4 to week 8) once in 4 weeks until the target maintenance dose of 1.0 mg was reached which was maintained for a period of 20 weeks. Total treatment period was 28 weeks.

Arm type	Experimental
Investigational medicinal product name	Semaglutide J, 1.34 mg/mL, 1.5 mL compact cartridge, PDS290
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.25, 0.5 or 1.0 mg once-weekly

Arm title	Semaglutide B

Arm description:

Subjects initially received 0.25 milligrams (mg) subcutaneous injections of semaglutide B once weekly and the dose was then escalated (0.25 mg in week 0 to week 4 and 0.5 mg in week 4 to week 8) once in 4 weeks until the target maintenance dose of 1.0 mg was reached which was maintained for a period of 20 weeks. Total treatment period was 28 weeks.

Arm type	Active comparator
Investigational medicinal product name	Semaglutide B, 1.34 mg/mL, 1.5 mL compact cartridge, PDS290
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.25, 0.5 or 1.0 mg once-weekly

Number of subjects in period 1	Semaglutide J	Semaglutide B
Started	291	97
Full analysis set (FAS)	291	97
Safety analysis set	291	97
Completed	283	91
Not completed	8	6
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	3
Physician decision	1	1
Lost to follow-up	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide J
Reporting group description:	
Subjects initially received 0.25 milligrams (mg) subcutaneous injections of semaglutide J once weekly and the dose was then escalated (0.25 mg in week 0 to week 4 and 0.5 mg in week 4 to week 8) once in 4 weeks until the target maintenance dose of 1.0 mg was reached which was maintained for a period of 20 weeks. Total treatment period was 28 weeks.	
Reporting group title	Semaglutide B
Reporting group description:	
Subjects initially received 0.25 milligrams (mg) subcutaneous injections of semaglutide B once weekly and the dose was then escalated (0.25 mg in week 0 to week 4 and 0.5 mg in week 4 to week 8) once in 4 weeks until the target maintenance dose of 1.0 mg was reached which was maintained for a period of 20 weeks. Total treatment period was 28 weeks.	

Reporting group values	Semaglutide J	Semaglutide B	Total
Number of subjects	291	97	388
Age Categorical Units: Subjects			
Adults (18-64 years)	291	96	387
From 65-84 years	0	1	1
Age Continuous Units: years			
arithmetic mean	53.7	54.8	
standard deviation	± 7.7	± 7.1	-
Gender Categorical Units: Subjects			
Female	128	47	175
Male	163	50	213
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	27	12	39
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	48	12	60
White	214	72	286
More than one race	2	0	2
Unknown or Not Reported	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	56	25	81
Not Hispanic or Latino	235	72	307
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Semaglutide J

Reporting group description:

Subjects initially received 0.25 milligrams (mg) subcutaneous injections of semaglutide J once weekly and the dose was then escalated (0.25 mg in week 0 to week 4 and 0.5 mg in week 4 to week 8) once in 4 weeks until the target maintenance dose of 1.0 mg was reached which was maintained for a period of 20 weeks. Total treatment period was 28 weeks.

Reporting group title	Semaglutide B

Reporting group description:

Subjects initially received 0.25 milligrams (mg) subcutaneous injections of semaglutide B once weekly and the dose was then escalated (0.25 mg in week 0 to week 4 and 0.5 mg in week 4 to week 8) once in 4 weeks until the target maintenance dose of 1.0 mg was reached which was maintained for a period of 20 weeks. Total treatment period was 28 weeks.

Primary: Change in glycosylated haemoglobin (HbA1c)

End point title	Change in glycosylated haemoglobin (HbA1c)

End point description:

Change in HbA1c from baseline (week 0) to end of treatment (week 28) is presented. The endpoint was evaluated based on the data from in-study period. The in-study period is defined as the uninterrupted time interval from date of randomisation to date of least contact with trial site. Full analysis set included all randomised subjects. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Primary

End point timeframe:

From baseline visit (visit 2; week 0) to end of treatment visit (visit 10; week 28)

End point values	Semaglutide J	Semaglutide B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	91		
Units: Percentage-point				
arithmetic mean (standard deviation)	-1.7 (± 1.0)	-1.6 (± 1.0)		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Full analysis set included all randomised participants. Here, "Overall Number of Participants Analyzed" signifies those participants who were evaluable for this outcome measure.

Comparison groups	Semaglutide J v Semaglutide B

Number of subjects included in analysis	376
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.08

Secondary: Number of Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Treatment Emergent Adverse Events (TEAEs)

End point description:

All presented adverse events are TEAE. A TEAE is defined as an adverse event with an onset date (or increase in severity) during the on-treatment observation period. On-treatment observation period is defined as from first drug date until the end of study. Safety analysis set included all subjects who are exposed to study intervention.

End point type	Secondary

End point timeframe:

From the time of first dosing to end of study visit (visit 11; week 33)

End point values	Semaglutide J	Semaglutide B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	97		
Units: Events				
number (not applicable)	408	120		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight

End point title	Change in body weight

End point description:

Change in body weight from baseline (week 0) to end of treatment (week 28) is presented. The endpoint was evaluated based on the data from in-study period. The in-study period is defined as the uninterrupted time interval from date of randomisation to date of least contact with trial site. Full analysis set included all randomised participants. Here, "Overall Number of Subjectss Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From baseline visit (visit 2; week 0) to end of treatment visit (visit 10; week 28)

End point values	Semaglutide J	Semaglutide B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	91		
Units: Kilogram (kg)				
arithmetic mean (standard deviation)	-5.0 (± 5.0)	-4.6 (± 4.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of anti-semaglutide antibodies (yes/no)

End point title	Occurrence of anti-semaglutide antibodies (yes/no)

End point description:

Occurrence of anti-semaglutide antibodies for in-study observation period is presented. The in-study period is defined as the uninterrupted time interval from date of randomisation to date of least contact with trial site. In the reported data 'yes' infers who received anti sema antibodies, whereas 'No' infers who did not receive anti sema antibodies. Safety analysis set included all subjects who are exposed to study intervention. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From baseline visit (visit 2; week 0) to end of study visit (visit 11; week 33)

End point values	Semaglutide J	Semaglutide B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	90		
Units: Subjects				
Yes	1	0		
No	281	90		

Statistical analyses

No statistical analyses for this end point

Secondary: Occurence of anti-semaglutide antibodies with in-vitro neutralising effect (Yes/no)

End point title	Occurence of anti-semaglutide antibodies with in-vitro neutralising effect (Yes/no)

End point description:

Occurrence of anti-semaglutide antibodies with in-vitro neutralizing effect was to be performed based on positive cross -reactivity to GLP-1. Since there was no sample with positive cross -reactivity to GLP-1, no further analysis was performed for invitro neutralizing effect towards native-GLP1. Therefore, no data

is available for this end point. In the reported data 'yes' infers who tested positive for anti-semaglutide antibodies whereas 'No' infers who tested negative for anti-semaglutide antibodies.

End point type	Secondary

End point timeframe:

From baseline visit (visit 2; week 0) to end of study visit (visit 11; week 33)

End point values	Semaglutide J	Semaglutide B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: Subjects				

Notes:

[1] - In-vitro neutralizing effect was not performed on samples with GLP-1 positive cross reactivity.

[2] - In-vitro neutralizing effect was not performed on samples with GLP-1 positive cross reactivity.

Statistical analyses

No statistical analyses for this end point

Secondary: Occurence of in-vitro neutralising cross-reacting antibodies to endogenous GLP-1 (Yes/no)

End point title	Occurence of in-vitro neutralising cross-reacting antibodies to endogenous GLP-1 (Yes/no)

End point description:

Occurence of in-vitro neutralising cross-reacting antibodies to endogenous GLP-1 from baseline (week 0) to week 33 is presented. In the reported data 'yes' infers who tested positive for in-vitro neutralising cross-reacting antibodies to endogenous GLP-1 whereas 'No' infers who tested negative for in-vitro neutralizing cross-reacting antibodies to endogenous GLP-1. Safety analysis set included all subjects who are exposed to study intervention. Here, "Overall Number of Subjectts Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From baseline visit (visit 2; week 0) to end of study visit (visit 11; week 33)

End point values	Semaglutide J	Semaglutide B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0[3]		
Units: Subjects				
Yes	0			
No	1			

Notes:

[3] - There were no subjects available for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Occurence of anti-semaglutide binding antibodies cross-reacting with

endogenous glucagon like peptide-1 (GLP-1) (Yes/no)

End point title	Occurence of anti-semaglutide binding antibodies cross-reacting with endogenous glucagon like peptide-1 (GLP-1) (Yes/no)

End point description:

Occurrence of anti-semaglutide binding antibodies cross-reacting with endogenous glucagon like peptide-1 (GLP-1) for in-study observation period is presented. The in-study period is defined as the uninterrupted time interval from date of randomisation to date of least contact with trial site. In the reported data 'yes' infers who tested positive for anti-semaglutide binding antibodies cross-reacting with endogenous glucagon like peptide-1 (GLP-1) whereas 'No' infers who tested negative for anti-semaglutide binding antibodies cross-reacting with endogenous glucagon like peptide-1 (GLP-1). Safety analysis set included all subjects who are exposed to study intervention. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From baseline visit (visit 2; week 0) to end of study visit (visit 11; week 33)

End point values	Semaglutide J	Semaglutide B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0[4]		
Units: Subjects				
Yes	0			
No	1			

Notes:

[4] - There were no subjects available for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-semaglutide antibodies level measured as percentage (%) Bound/Total

End point title	Anti-semaglutide antibodies level measured as percentage (%) Bound/Total

End point description:

Anti-semaglutide antibodies level measured as %Bound/Total from baseline (week 0) to week 33 is presented. Safety analysis set included all subjects who are exposed to study intervention. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From baseline visit (visit 2; week 0) to end of study visit (visit 11; week 33)

End point values	Semaglutide J	Semaglutide B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0[5]		
Units: %Bound/Total				
arithmetic mean (standard deviation)	3.47 (± 0.00)	()		

Notes:

[5] - There were no subjects available for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-semaglutide antibodies level (measured as titre)

End point title	Anti-semaglutide antibodies level (measured as titre)

End point description:

Anti-semaglutide antibodies level measured as titre from baseline (week 0) to week 33 is presented. Safety analysis set included all subjects who are exposed to study intervention. Here, "Overall Number of Subjects Analyzed" signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

From baseline visit (visit 2; week 0) to end of study visit (visit 11; week 33)

End point values	Semaglutide J	Semaglutide B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	0[6]		
Units: Titre				
arithmetic mean (standard deviation)	15.00 (± 0.00)	()		

Notes:

[6] - There were no subjects available for analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of first dosing (week 0) to end of study (week 33).

Adverse event reporting additional description:

Treatment emergent adverse events presented, defined as adverse events with onset date (or increase in severity) during on-treatment observation period, defined as from 1st drug date until end of study. Safety analysis set: all participants who are exposed to study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	Semaglutide B

Reporting group description:

Participants initially received 0.25 milligrams (mg) subcutaneous injections of semaglutide B once weekly and the dose was then escalated (0.25 mg in week 0 to week 4 and 0.5 mg in week 4 to week 8) once in 4 weeks until the target maintenance dose of 1.0 mg was reached which was maintained for a period of 20 weeks. Total treatment period was 28 weeks.

Reporting group title	Semaglutide J

Reporting group description:

Participants initially received 0.25 milligrams (mg) subcutaneous injections of semaglutide J once weekly and the dose was then escalated (0.25 mg in week 0 to week 4 and 0.5 mg in week 4 to week 8) once in 4 weeks until the target maintenance dose of 1.0 mg was reached which was maintained for a period of 20 weeks. Total treatment period was 28 weeks.

Serious adverse events	Semaglutide B	Semaglutide J	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 97 (5.15%)	8 / 291 (2.75%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign salivary gland neoplasm			
subjects affected / exposed	0 / 97 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 97 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	1 / 97 (1.03%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 97 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 97 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	0 / 97 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 97 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 97 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Umbilical hernia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 97 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 97 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 97 (1.03%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Semaglutide B	Semaglutide J	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 97 (24.74%)	64 / 291 (21.99%)	
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 97 (2.06%)	17 / 291 (5.84%)	
occurrences (all)	2	19	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 97 (7.22%)	26 / 291 (8.93%)	
occurrences (all)	8	32	
Nausea			
subjects affected / exposed	15 / 97 (15.46%)	35 / 291 (12.03%)	
occurrences (all)	18	58	
Vomiting			
subjects affected / exposed	5 / 97 (5.15%)	15 / 291 (5.15%)	
occurrences (all)	5	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2022	This version of the protocol is prepared to include additional PK samples and analyses to allow PK comparability of semaglutide J s.c. and semaglutide B s.c., based on the Health Canada's feedback.Population pharmacokinetics will be addressed in a modelling analysis plan and the totality of evidence from all PK assessments will be presented as a collective whole in a comprehensive modelling report. Therefore, secondary PK objective has been removed from the protocol.
06 December 2022	This change has been made to increase the robustness and acceptability of the primary assessment and is based on recommendations from Health Authority. This is to maintain 80% power under the non-inferiority analysis that does not utilize historical data. This has been done to simplify and provide more clarity. This has been done to correct spelling mistake.This has been removed as it is no longer defined in the protocol.
07 June 2023	This has been done to correct wrong specification. This has been done in accordance with feedback received from health authority. This has been done in accordance with the change of the estimands. This has been done to preserve the conservatism of the primary analysis and is aligned with feedback received from health authority. This has been done to correct the time range for sampling. This has been done to maintain consistency between Section 4.3 and Section 6.1. This has been removed as it is no longer defined in protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported