Clinical trial results:
A randomized placebo-controlled study in patients with a Gallium-68 DOTATATE PET/CT positive, clinically non-functioning pituitary macroadenoma (NFMA) of the effect of Lanreotide autosolution on Tumor (adenoma) size

Summary

EudraCT number	2015-001234-22
Trial protocol	NL
Global end of trial date	26 May 2021

Results information

Result version number	v1 (current)
This version publication date	07 February 2025
First version publication date	07 February 2025
Summary attachment (see zip file)	Trial publication in The Lancet Regional Health - Europe (Boertien et al 2024 - Lanreotide versus placebo for tumour reduction ....pdf)

Trial information

Trial identification

Sponsor protocol code	NL52821.018.15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Nederlands Trial Register: NTR5275, National Trial Register (new): NL5136

Notes:

Sponsors

Sponsor organisation name	Academic Medical Center
Sponsor organisation address	Meibergdreef 9, Amsterdam, Netherlands, 1105 AZ
Public contact	Eric Fliers, principal investigator, Academic Medical Center (currently part of Amsterdam UMC), 0031 205666071, e.fliers@amsterdamumc.nl
Scientific contact	Eric Fliers, principal investigator, Academic Medical Center (currently part of Amsterdam UMC), 0031 205666071, e.fliers@amsterdamumc.nl

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	28 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 May 2021
Global end of trial reached?	Yes
Global end of trial date	26 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of lanreotide autosolution during 72 weeks, as compared to placebo, on tumour size in patients with a non-functioning pituitary macroadenoma and positive pituitary somatostatin receptor imaging using Gallium-68 DOTATATE PET/CT.
Note that our planned number of subjects was 66, as the percentage of positive Gallium-68 DOTATATE uptake was unknown and only those with positive uptake would be randomized for treatment. The final number of enrolled patients was 49 in order to be able to randomize 44 subjects between lanreotide and placebo.

Protection of trial subjects:

The study was approved by the ethics committe and conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All trial subjects were informed in full on the trial details, and received information in writing before providing informed consent. Privacy rules regarding collection and storing of medical and personal data were adhered to. Insurance was in place in case of damage caused by participation in the study. Trial subjects could withdraw from the study at any time and for any reason. All adverse events were recorded and followed up, and if necessary, subjects were withdrawn for medical reasons.

Background therapy:

Subjects who had undergone previous adenoma surgery were eligible for inclusion, as long as the tumour remnant was >1cm in size.

Evidence for comparator:

The comparator in our study is placebo.

Actual start date of recruitment	03 November 2015
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	Netherlands: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	31
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place between 3 November 2015 and 10 December 2019. The study was conducted in an outpatient setting and eligible patients were referred by endocrinologists at academic and non-academic hospitals in the Netherlands for inclusion at one of the participating centres.

Pre-assignment

Screening details:

After inclusion and informed consent, all participants underwent the study 68Ga-DOTATATE PET-CT. Only those participants with positive tracer uptake within the adenoma were randomised for study treatment.

Pre-assignment period milestones

Number of subjects started	49
Intermediate milestone: Number of subjects	68Ga-DOTATATE PET-CT scan: 49
Number of subjects completed	44

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	negative 68Ga-DOTATATE PET: 4

Period 1

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

Blinding implementation details:

The randomisation list was stored in a secure trial file at the Pharmacy and was only disclosed after database lock. As the prefilled lanreotide syringes differed in appearance from the placebo, injections were administered by trained, independent nurses who were unmasked to treatment allocation, a method also used in previous trials. To maintain blinding during transport, prepared study medication was placed in an opaque bag within a sealed cardboard box.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lanreotide

Arm description:

Treatment with lanreotide acetate 120mg (Somatuline AutoSolution, Ipsen Farmaceutica BV; known outside the Netherlands as Somatuline Autogel), without dose titration.

Arm type	Active comparator
Investigational medicinal product name	Somatuline Autosolution
Investigational medicinal product code	PR1
Other name	lanreotide acetate, Somatuline Autogel
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use, Solution for injection

Dosage and administration details:

Pre-filled syringes with dosage of 120mg (volume 0.4mL), administered every 28 days as a deep subcutaneous injection into the superior, external quadrant of the buttock.

Arm title	Placebo

Arm description:

Treatment with placebo, consisting of saline 0.9%

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	saline 0.9%
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Solution for injection , Subcutaneous use

Dosage and administration details:

Solution of saline (sodium chloride 0.9%), delivered in plastic bottle with syringe and needle. Trained nurses drew up 0.4 mL (matching the Somatuline Autosolution volume) to prepare the injection for administration. Injections were administered every 28 days as a deep subcutaneous injection into the superior, external quadrant of the buttock.

Number of subjects in period 1[1]	Lanreotide	Placebo
Started	22	22
24 week visit	19	22
48 week visit	16	20
Completed	13	19
Not completed	9	3
Adverse event, non-fatal	4	-
Lack of efficacy	3	3
Protocol deviation	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: After inclusion and informed consent, all 49 participants underwent the study 68Ga-DOTATATE PET-CT. Only those participants with positive tracer uptake within the adenoma were randomised for study treatment and formed the overall trial (and are thus reported in the baseline period), this number is 44 as prespecified in the power calculation.

Baseline characteristics

Reporting groups	
Reporting group title	Lanreotide
Reporting group description:	
Treatment with lanreotide acetate 120mg (Somatuline AutoSolution, Ipsen Farmaceutica BV; known outside the Netherlands as Somatuline Autogel), without dose titration.	
Reporting group title	Placebo
Reporting group description:	
Treatment with placebo, consisting of saline 0.9%	

Reporting group values	Lanreotide	Placebo	Total
Number of subjects	22	22	44
Age categorical			
Units: Subjects			
Adults (18-64 years)	15	11	26
From 65-84 years	7	11	18
Age continuous			
Units: years			
arithmetic mean	58.8	63.5	
standard deviation	± 8.2	± 8.5	-
Gender categorical			
Units: Subjects			
Female	10	6	16
Male	12	16	28
Any pituitary hormone deficiency			
Units: Subjects			
No	7	11	18
Yes	15	11	26
Previous NFPMA resection			
At any time before study participation. NFPMA = non-functioning pituitary macroadenoma			
Units: Subjects			
No	7	13	20
Yes	15	9	24
Centre of inclusion			
Units: Subjects			
Amsterdam UMC location AMC	15	16	31
Amsterdam UMC location VUmc	1	3	4
Leiden University Medical Centre (LUMC)	6	3	9
Baseline NFPMA cranio-caudal diameter			
NFPMA=non-functioning pituitary macroadenoma			
Units: millimetre(s)			
median	16.2	16.3	
inter-quartile range (Q1-Q3)	13.4 to 20.6	14.8 to 19.3	-
Baseline NFPMA tumour volume			
NFPMA = non-functioning pituitary macroadenoma			
Units: cubic millimeter			
median	2782	2722	

inter-quartile range (Q1-Q3)	1868 to 4067	1937 to 3967	-
68Ga-DOTATATE PET NFPMA SUVmean			
The mean standard uptake value measured within the adenoma. SUV is an unitless value. NFPMA=non-functioning pituitary macroadenoma. PET=positron emission tomography. SUV=standard uptake value.			
Units: unit(s)			
median	6.1	5.0	
inter-quartile range (Q1-Q3)	3.2 to 8.1	2.7 to 6.7	-
68Ga-DOTATATE PET NFPMA SUVmax			
The maximum standard uptake value measured within the adenoma. SUV is a unitless value. NFPMA=non-functioning pituitary macroadenoma. PET=positron emission tomography. SUV=standard uptake value.			
Units: unit(s)			
median	7.9	6.4	
inter-quartile range (Q1-Q3)	5.0 to 11.0	3.5 to 9.1	-

Subject analysis sets

Subject analysis set title	All included participants
Subject analysis set type	Full analysis

Subject analysis set description:

Clinical characteristics of all participants with 68Ga-DOTATATE PET-positive and PET-negative adenoma. Only PET-positive participants were randomised to study treatment. Note: there is no centrally assessed baseline or end tumour size (cranio-caudal diameter and tumour volume) data for this subject analysis set.

Subject analysis set title	Per-protocol population - lanreotide group
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population included participants who completed study treatment with all 18 injections and underwent week-72 MRI (deviations in visit time windows were allowed). This set comprises participants in the lanreotide group who completed the study (n=13).

Subject analysis set title	Per-protocol population - placebo group
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol population included participants who completed study treatment with all 18 injections and underwent week-72 MRI (deviations in visit time windows were allowed). This set comprises participants in the placebo group who completed the study (n=19).

Reporting group values	All included participants	Per-protocol population - lanreotide group	Per-protocol population - placebo group
Number of subjects	49	13	19
Age categorical			
Units: Subjects			
Adults (18-64 years)	31		
From 65-84 years	18		
Age continuous			
Units: years			
arithmetic mean	59.3		
standard deviation	± 10.2	±	±
Gender categorical			
Units: Subjects			
Female	18		
Male	31		

Any pituitary hormone deficiency Units: Subjects			
No	20		
Yes	29		
Previous NFPMA resection			
At any time before study participation. NFPMA = non-functioning pituitary macroadenoma			
Units: Subjects			
No	23		
Yes	26		
Centre of inclusion Units: Subjects			
Amsterdam UMC location AMC	34		
Amsterdam UMC location VUmc	5		
Leiden University Medical Centre (LUMC)	10		
Baseline NFPMA cranio-caudal diameter			
NFPMA=non-functioning pituitary macroadenoma			
Units: millimetre(s) median inter-quartile range (Q1-Q3)			
Baseline NFPMA tumour volume			
NFPMA = non-functioning pituitary macroadenoma			
Units: cubic millimeter median inter-quartile range (Q1-Q3)			
68Ga-DOTATATE PET NFPMA SUVmean			
The mean standard uptake value measured within the adenoma. SUV is an unitless value. NFPMA=non-functioning pituitary macroadenoma. PET=positron emission tomography. SUV=standard uptake value.			
Units: unit(s) median inter-quartile range (Q1-Q3)	 5.4 2.9 to 7.2		
68Ga-DOTATATE PET NFPMA SUVmax			
The maximum standard uptake value measured within the adenoma. SUV is a unitless value. NFPMA=non-functioning pituitary macroadenoma. PET=positron emission tomography. SUV=standard uptake value.			
Units: unit(s) median inter-quartile range (Q1-Q3)	 7.0 3.5 to 9.6		

End points

End points reporting groups

Reporting group title	Lanreotide
Reporting group description:	
Treatment with lanreotide acetate 120mg (Somatuline AutoSolution, Ipsen Farmaceutica BV; known outside the Netherlands as Somatuline Autogel), without dose titration.	
Reporting group title	Placebo
Reporting group description:	
Treatment with placebo, consisting of saline 0.9%	
Subject analysis set title	All included participants
Subject analysis set type	Full analysis
Subject analysis set description:	
Clinical characteristics of all participants with 68Ga-DOTATATE PET-positive and PET-negative adenoma. Only PET-positive participants were randomised to study treatment. Note: there is no centrally assessed baseline or end tumour size (cranio-caudal diameter and tumour volume) data for this subject analysis set.	
Subject analysis set title	Per-protocol population - lanreotide group
Subject analysis set type	Per protocol
Subject analysis set description:	
The per-protocol population included participants who completed study treatment with all 18 injections and underwent week-72 MRI (deviations in visit time windows were allowed). This set comprises participants in the lanreotide group who completed the study (n=13).	
Subject analysis set title	Per-protocol population - placebo group
Subject analysis set type	Per protocol
Subject analysis set description:	
The per-protocol population included participants who completed study treatment with all 18 injections and underwent week-72 MRI (deviations in visit time windows were allowed). This set comprises participants in the placebo group who completed the study (n=19).	

Primary: Change in cranio-caudal diameter

End point title	Change in cranio-caudal diameter
End point description:	
End point type	Primary
End point timeframe:	
Primary outcome was the change in cranio-caudal tumour diameter from baseline to week-72 or treatment discontinuation.	

End point values	Lanreotide	Placebo	Per-protocol population - lanreotide group	Per-protocol population - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	22	22	13	19
Units: millimetre(s)				
arithmetic mean (standard deviation)	1.2 (± 2.5)	1.3 (± 1.5)	1.3 (± 3.0)	1.2 (± 1.6)

Attachments (see zip file)	Primary outcome main, additional & sensitivity ana/Table S3. Change in tumour size from baseline to end-of-trea/Fig S1. Primary&secondary tumour size outcomes in ITT & PP/Table 2

Statistical analyses

Statistical analysis title	Primary outcome main analysis (ITT population)

Statistical analysis description:

For the main analysis of the primary outcome change in cranio-caudal diameter, all data up to treatment discontinuation was included (ie, 'while-on-treatment' strategy). An analysis of covariance (ANCOVA) model was used to control for any chance imbalance in baseline size between groups, with end-of-treatment measurement as dependent variable, baseline measurement as continuous covariate, and treatment as categorical covariate.

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93 [1]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	0.6

Notes:

[1] - The statistical significance level for analyses was set at p = 0·05 (two-sided). There was no need for multiplicity adjustments.

Statistical analysis title	Primary outcome in per-protocol population

Statistical analysis description:

For the analysis of the primary outcome change in cranio-caudal diameter in the per-protocol population an analysis of covariance (ANCOVA) model was used to control for any chance imbalance in baseline size between groups, with end-of-treatment measurement as dependent variable, baseline measurement as continuous covariate, and treatment as categorical covariate.

Comparison groups	Per-protocol population - placebo group v Per-protocol population - lanreotide group
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.8
Variability estimate	Standard error of the mean
Dispersion value	0.8

Statistical analysis title	Primary outcome multiple imputation missing data

Statistical analysis description:

A supplementary efficacy analysis applied univariate multiple imputation to impute missing week-72 MRI data, assuming missingness at random (MAR). Data were imputed separately in each treatment group using a regression model, and 27 imputed datasets were generated (corresponding to 27% of missing week-72 data). Each dataset was assessed with the earlier specified ANCOVA model and results were pooled using Rubin's rules.

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	1.97
Variability estimate	Standard error of the mean
Dispersion value	0.82

Statistical analysis title	Pattern-mixture model (sensitivity), δ= +0.317mm

Statistical analysis description:

Sensitivity analysis via pattern-mixture model to explore departures from missing-at-random (MAR) assumption and address potential bias due to differential dropout between treatment groups. The imputed MAR data was shifted by a range of offsets (δ, delta) to assess alternative post-dropout scenarios of tumour behaviour. Results under MAR were considered robust if an observed treatment effect was qualitatively maintained for a range of plausible offsets.

Comparison groups	Placebo v Lanreotide
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	2.08
Variability estimate	Standard error of the mean
Dispersion value	0.83

Statistical analysis title	Pattern-mixture model (sensitivity), δ= +0.634mm

Statistical analysis description:

Sensitivity analysis via pattern-mixture model to explore departures from missing-at-random (MAR) assumption and address potential bias due to differential dropout between treatment groups. The imputed MAR data was shifted by a range of offsets (δ, delta) to assess alternative post-dropout scenarios of tumour behaviour. Results under MAR were considered robust if an observed treatment effect was qualitatively maintained for a range of plausible offsets.

Comparison groups	Placebo v Lanreotide
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	2.18
Variability estimate	Standard error of the mean
Dispersion value	0.83

Statistical analysis title	Pattern-mixture model (sensitivity), δ= +0.950mm

Statistical analysis description:

Sensitivity analysis via pattern-mixture model to explore departures from missing-at-random (MAR) assumption and address potential bias due to differential dropout between treatment groups. The imputed MAR data was shifted by a range of offsets (δ, delta) to assess alternative post-dropout scenarios of tumour behaviour. Results under MAR were considered robust if an observed treatment effect was qualitatively maintained for a range of plausible offsets.

Comparison groups	Placebo v Lanreotide
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	0.84

Statistical analysis title	Pattern-mixture model (sensitivity), δ= +1.267mm

Statistical analysis description:

Sensitivity analysis via pattern-mixture model to explore departures from missing-at-random (MAR) assumption and address potential bias due to differential dropout between treatment groups. The imputed MAR data was shifted by a range of offsets (δ, delta) to assess alternative post-dropout scenarios of tumour behaviour. Results under MAR were considered robust if an observed treatment effect was qualitatively maintained for a range of plausible offsets.

Comparison groups	Placebo v Lanreotide
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	2.41
Variability estimate	Standard error of the mean
Dispersion value	0.85

Statistical analysis title	Pattern-mixture model (sensitivity), δ= +2.534mm

Statistical analysis description:

Sensitivity analysis via pattern-mixture model to explore departures from missing-at-random (MAR) assumption and address potential bias due to differential dropout between treatment groups. The imputed MAR data was shifted by a range of offsets (δ, delta) to assess alternative post-dropout scenarios of tumour behaviour. Results under MAR were considered robust if an observed treatment effect was qualitatively maintained for a range of plausible offsets.

Comparison groups	Placebo v Lanreotide
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	2.9
Variability estimate	Standard error of the mean
Dispersion value	0.91

Statistical analysis title	Tipping point analysis, δ= -5.385mm for lanreotide

Statistical analysis description:

A tipping-point analysis explored which δ-shift was needed to overturn the conclusion of the main analysis (ie, in which alternative post-dropout scenario would treatment effect be statistically significant). This involved subtracting increasing percentages of the mean change from the MAR imputed data in the lanreotide group until the resulting treatment effect following ANCOVA was statistically significant. The required δ of -5.385mm was considered clinically highly implausible.

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	3.78
Variability estimate	Standard error of the mean
Dispersion value	0.96

Statistical analysis title	Linear mixed effects model

Statistical analysis description:

Linear mixed effects model to account for repeated MRI measurements obtained at varying time-points. Post-baseline cranio-caudal diameter was modelled with treatment group, measurement time, groupby time interaction, baseline cranio-caudal diameter, and baseline diameterbytime interaction as fixed effects, a by-subject random intercept, and a first-order autoregressive residual autocorrelation structure. Treatment effect was estimated as the contrast between adjusted group means at final time

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.82 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	1.03
Variability estimate	Standard error of the mean
Dispersion value	0.58

Notes:

[2] - The final model was modified post-hoc to include the additional fixed effects of baseline cranio-caudal diameter and baseline diameterbytime interaction to correctly adjust for baseline size; the outcome/response vector was adjusted to only contain post-baseline measurements. As an additional post-hoc optimisation, a residual correlation matrix was specified to address possible residual serial autocorrelation not sufficiently accounted for by the random intercept.
[3] - Treatment effect estimated as the contrast between treatment groups at final measurement time (corresponding to week-72) using R emmeans package, based on leastsquare means with Satterthwaite method for approximation of degrees of freedom

Statistical analysis title	Mixed model for repeated measurements (MMRM)

Statistical analysis description:

Data were fitted post-hoc with a MMRM to relax the LME assumption of linear time trends, with time as categorical variable and an unstructured covariance matrix to model within-patient residual errors. This required 'simplification' of post-baseline time data to a factor with only 4 levels: time1=measurement obtained before week-24 visit, time2=week-24 visit, time3=measurement obtained between week-24 and week-72 visit, and time4=week-72 (end) visit.

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority[4]
P-value	= 0.92 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	1.44
Variability estimate	Standard error of the mean
Dispersion value	0.75

Notes:

[4] - The model included the fixed effects of group, time, groupbytime interaction, baseline size, and baseline sizebytime interaction; and an unstructured covariance matrix to model within-patient residual errors.
[5] - Treatment effect estimated as the contrast between treatment groups at end visit (corresponding to week-72) using R emmeans package, based on leastsquare means with Satterthwaite method for approximation of degrees of freedom

Secondary: Change in tumour volume

End point title	Change in tumour volume

End point description:

End point type	Secondary

End point timeframe:

The change in tumour volume from baseline to week-72 or treatment discontinuation.

End point values	Lanreotide	Placebo	Per-protocol population - lanreotide group	Per-protocol population - placebo group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	22	22	13	19
Units: cubic millimeter				
median (inter-quartile range (Q1-Q3))	424 (61 to 811)	181 (19 to 738)	590 (91 to 828)	260 (26 to 1049)

Statistical analyses

Statistical analysis title	Tumour volume main analysis (ITT population)

Statistical analysis description:

For the main analysis of the secondary outcome change in tumour volume, all data up to treatment discontinuation was included (ie, 'while-on-treatment' strategy). An analysis of covariance (ANCOVA) model was used to control for any chance imbalance in baseline size between groups, with end-of-treatment measurement as dependent variable, baseline measurement as continuous covariate, and treatment as categorical covariate.

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 [6]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-422
upper limit	486

Notes:

[6] - Tumour volume values were natural log-transformed before analysis due to non-normal distribution with moderate positive skewness, the back-transformed estimated mean difference and 95% CI are reported.

Statistical analysis title	Tumour volume per-protocol population

Statistical analysis description:

For the analysis of the secondary outcome change in tumour volume in the per-protocol population an analysis of covariance (ANCOVA) model was used to control for any chance imbalance in baseline size between groups, with end-of-treatment measurement as dependent variable, baseline measurement as continuous covariate, and treatment as categorical covariate.

Comparison groups	Per-protocol population - lanreotide group v Per-protocol population - placebo group
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94 [7]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-657
upper limit	706
Variability estimate	Standard error of the mean
Dispersion value	333

Notes:

[7] - Tumour volume values in the per-protocol population were sufficiently normally distributed and thus not (natural log) transformed for analysis.

Secondary: Time to tumour volume progression

End point title	Time to tumour volume progression

End point description:

Tumour progression was defined as clinically significant increase in tumour volume of ≥20%.

End point type	Secondary

End point timeframe:

Time to progression was defined as the interval in weeks between start of study treatment and the first subsequent MRI scan showing a clinically significant increase in tumour volume, counting events in each group.

End point values	Lanreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: events	9	5		

Attachments (see zip file)	Kaplan-Meier estimates of time to tumour progressi/Fig 2.

Statistical analyses

Statistical analysis title	Time to progression in tumour volume

Statistical analysis description:

Time to progression compared between groups with stratified log-rank test, with stratification for presence or absence of documented tumour growth at baseline. Hazard ratio derived from a Cox proportional-hazards model with terms for study treatment and tumour growth at baseline; with no statistically significant interaction between these terms. There were 9 events in placebo group (median time to progression 72 wks, 95% CI not reached), and 5 events in placebo group (median time not reached).

Comparison groups	Placebo v Lanreotide
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11 [8]
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.37

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	7.15

Notes:

[8] - Stratified log-rank test, with stratification for presence or absence of documented tumour growth at baseline.

Secondary: Change in SF-36 component score physical functioning

End point title	Change in SF-36 component score physical functioning

End point description:

End point type	Secondary

End point timeframe:

The change in quality of life based on SF-36 component score physical functioning (PF) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

End point values	Lanreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: unit(s)				
arithmetic mean (standard deviation)	-0.4 (± 16.1)	-5.5 (± 16.1)		

Attachments (see zip file)	Spider plots of mean SF-36 component scores /Fig S3. SF-36 Change in SF-36 component scores/Table S4. Change in quality

Statistical analyses

Statistical analysis title	Change in SF-36 physical functioning

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation.

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	14.2
Variability estimate	Standard error of the mean
Dispersion value	5.2

Secondary: Change in SF-36 component score limitations physical health

End point title	Change in SF-36 component score limitations physical health

End point description:

End point type	Secondary

End point timeframe:

The change in quality of life based on SF-36 component score role limitations due to physical health problems (RP) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

End point values	Lanreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: unit(s)				
arithmetic mean (standard deviation)	-12.0 (± 26.9)	-4.8 (± 36.5)		

Statistical analyses

Statistical analysis title	Change in SF-36 limitations physical

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation.

Comparison groups	Placebo v Lanreotide
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.2
upper limit	9.9

Variability estimate	Standard error of the mean
Dispersion value	9.4

Secondary: Change in SF-36 component score bodily pain

End point title	Change in SF-36 component score bodily pain

End point description:

End point type	Secondary

End point timeframe:

The change in quality of life based on SF-36 component score bodily pain (BP) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

End point values	Lanreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: unit(s)				
arithmetic mean (standard deviation)	-8.5 (± 26.1)	-2.9 (± 13.7)		

Statistical analyses

Statistical analysis title	Change in SF-36 bodily pain

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation.

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	5.7
Variability estimate	Standard error of the mean
Dispersion value	6.1

Secondary: Change in SF-36 component score general health

End point title	Change in SF-36 component score general health

End point description:

End point type	Secondary

End point timeframe:

The change in quality of life based on SF-36 component score general health perceptions (GH) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

End point values	Lanreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: unit(s)				
arithmetic mean (standard deviation)	-1.6 (± 13.7)	-1.1 (± 12.0)		

Statistical analyses

Statistical analysis title	Change in SF-36 general health

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation.

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3
upper limit	7.1
Variability estimate	Standard error of the mean
Dispersion value	4.1

Secondary: Change in SF-36 component score vitality

End point title	Change in SF-36 component score vitality

End point description:

End point type	Secondary

End point timeframe:

The change in quality of life based on SF-36 component score vitality (VT) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

End point values	Lanreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: unit(s)				
arithmetic mean (standard deviation)	-5.4 (± 17.3)	-0.9 (± 12.7)		

Statistical analyses

Statistical analysis title	Change in SF-36 vitality

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation.

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.8
upper limit	2.9
Variability estimate	Standard error of the mean
Dispersion value	4.6

Secondary: Change in SF-36 component score social functioning

End point title	Change in SF-36 component score social functioning

End point description:

End point type	Secondary

End point timeframe:

The change in quality of life based on SF-36 component score social functioning (SF) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

End point values	Lanreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: unit(s)				
arithmetic mean (standard deviation)	-5.6 (± 22.0)	-4.5 (± 14.2)		

Statistical analyses

Statistical analysis title	Change in SF-36 social functioning

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation.

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	8.8
Variability estimate	Standard error of the mean
Dispersion value	5.8

Secondary: Change in SF-36 component score limitations emotional

End point title	Change in SF-36 component score limitations emotional

End point description:

End point type	Secondary

End point timeframe:

The change in quality of life based on SF-36 component score role limitations due to emotional problems (RE) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

End point values	Lanreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: unit(s)				
arithmetic mean (standard deviation)	-8.7 (± 30.9)	-6.1 (± 24.4)		

Statistical analyses

Statistical analysis title	Change in SF-36 limitations emotional

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.4
upper limit	10.9
Variability estimate	Standard error of the mean
Dispersion value	8.5

Secondary: Change in SF-36 component score general mental health

End point title	Change in SF-36 component score general mental health

End point description:

End point type	Secondary

End point timeframe:

The change in quality of life based on SF-36 component score general mental health (MH) from baseline to week-72 or treatment discontinuation. The scores are converted to 0-100 unitless scale.

End point values	Lanreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: unit(s)				
arithmetic mean (standard deviation)	-4.9 (± 13.4)	0.2 (± 6.8)		

Statistical analyses

Statistical analysis title	Change in SF-36 general mental health

Statistical analysis description:

Change from baseline in component scores was compared between groups using ANCOVA with end-of-treatment score as dependent variable, baseline score as continuous covariate, and treatment as categorical covariate. The mean imputation method was used to replace missing component score values up to treatment discontinuation.

Comparison groups	Lanreotide v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	3.3

Other pre-specified: Tumour volume percentage change

End point title	Tumour volume percentage change

End point description:

End point type	Other pre-specified

End point timeframe:

Percentage change in tumour volume from baseline measurement to week 72 or treatment discontinuation. No between-group analysis performed on this end point.

End point values	Lanreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: percent				
median (inter-quartile range (Q1-Q3))	17.2 (1.5 to 29.7)	7.8 (0.7 to 16.2)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Time to tumour volume or cranio-caudal diameter progression

End point title	Time to tumour volume or cranio-caudal diameter progression

End point description:

Tumour progression was defined as clinically significant increase of either in tumour volume (≥20%) or cranio-caudal diameter (≥2 mm) on any subsequent MRI scan past baseline.

End point type	Post-hoc

End point timeframe:

Time to progression was defined as the interval in weeks between start of study treatment and the first subsequent MRI scan showing a clinically significant increase in tumour volume or cranio-caudal diameter, counting events in each group.

End point values	Lanreotide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: events	11	9		

Attachments (see zip file)	Kaplan-Meier estimates of time to tumour progressi/Fig S2.

Statistical analyses

Statistical analysis title	Time to tumour progression

Statistical analysis description:

Time to progression compared between groups with stratified log-rank test, with stratification for presence or absence of documented tumour growth at baseline. Hazard ratio derived from a Cox proportional-hazards model with terms for study treatment and tumour growth at baseline; with no statistically significant interaction between these terms. There were 11 events in lanreotide group (median time to progression 72 wks, 95% CI 50.6-83.4), and 9 events in placebo group (median time not reached).

Comparison groups	Lanreotide v Placebo

Number of subjects included in analysis	44
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.25 [9]
Method	Stratified log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	4.15

Notes:

[9] - Stratified log-rank test, with stratification for presence or absence of documented tumour growth at baseline.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any undesirable event, finding, or change from baseline (eg, worsening of known dyspepsia) occurring between study enrolment and up to 30 days after treatment completion or discontinuation was considered an adverse event.

Adverse event reporting additional description:

AEs were assessed systematically at each study visit (via i.a. a fasting blood sample, measurement of vitals, and a semi-structured interview focused on AEs/side effects). Non-systematically assessed AEs (through self-reporting at any time during study participation) are not reported here, but have been published.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Lanreotide

Reporting group description:

Treatment with lanreotide acetate 120mg (Somatuline AutoSolution, Ipsen Farmaceutica BV; known outside the Netherlands as Somatuline Autogel), without dose titration.

Reporting group title	Placebo

Reporting group description:

Treatment with placebo, consisting of saline 0.9%

Serious adverse events	Lanreotide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 22 (27.27%)	3 / 22 (13.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Hospital admission for observation after bike accident			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospital admission for planned adenoma resection			
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospital admission for planned ileocecal resection due to			

complicated Crohn's disease			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hospital admission for analysis of chest pain and/or dyspnoea	Additional description: Critical conditions such as pulmonary embolism or myocardial ischemia were ruled out.		
subjects affected / exposed	3 / 22 (13.64%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Lanreotide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	21 / 22 (95.45%)	
Investigations			
Insulin-like growth factor decreased	Additional description: Age-adjusted IGF-1 SDS below -2·0		
subjects affected / exposed	4 / 22 (18.18%)	0 / 22 (0.00%)	
occurrences (all)	4	0	
Weight decreased	Additional description: Unintentional weight loss		
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Thyroxine free decreased	Additional description: Free thyroxine below lower limit of normal		
subjects affected / exposed	6 / 22 (27.27%)	1 / 22 (4.55%)	
occurrences (all)	6	1	
Liver function test increased	Additional description: Comprising alanine aminotransferase or gamma-glutamyltransferase >2 times the upper limit of normal or alkaline phosphatase >20 U/L above the upper limit of normal		
subjects affected / exposed	4 / 22 (18.18%)	2 / 22 (9.09%)	
occurrences (all)	4	2	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	22	
Cardiac disorders			
Bradycardia	Additional description: defined as <60 beats per minute		

subjects affected / exposed	4 / 22 (18.18%)	0 / 22 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Dizziness	Additional description: Dizziness or light-headedness		
subjects affected / exposed	2 / 22 (9.09%)	3 / 22 (13.64%)	
occurrences (all)	2	3	
Headache			
subjects affected / exposed	7 / 22 (31.82%)	4 / 22 (18.18%)	
occurrences (all)	7	4	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	12 / 22 (54.55%)	0 / 22 (0.00%)	
occurrences (all)	12	0	
Fatigue			
subjects affected / exposed	5 / 22 (22.73%)	3 / 22 (13.64%)	
occurrences (all)	5	3	
Eye disorders			
Visual impairment	Additional description: Visual complaints or disturbances		
subjects affected / exposed	3 / 22 (13.64%)	3 / 22 (13.64%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Abdominal pain	Additional description: Complaints of abdominal pain, discomfort, cramps		
subjects affected / exposed	10 / 22 (45.45%)	2 / 22 (9.09%)	
occurrences (all)	10	2	
Frequent bowel movements	Additional description: Increased stool frequency or diarrhoea		
subjects affected / exposed	16 / 22 (72.73%)	4 / 22 (18.18%)	
occurrences (all)	16	4	
Nausea	Additional description: nausea or dyspepsia		
subjects affected / exposed	8 / 22 (36.36%)	1 / 22 (4.55%)	
occurrences (all)	8	1	
Decreased appetite			
subjects affected / exposed	2 / 22 (9.09%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Flatulence			
subjects affected / exposed	3 / 22 (13.64%)	1 / 22 (4.55%)	
occurrences (all)	3	1	

Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Any complaint of increased hair loss or decreased hair growth		
subjects affected / exposed	5 / 22 (22.73%)	0 / 22 (0.00%)	
occurrences (all)	5	0	
Endocrine disorders			
Impaired fasting glucose	Additional description: Defined as fasting glucose level of 5.7–6.9 mmol/L		
subjects affected / exposed	10 / 22 (45.45%)	3 / 22 (13.64%)	
occurrences (all)	10	3	
Hyperglycaemia	Additional description: Defined as glucose level ≥7 mmol/L		
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2016	- Leiden University Medical Centre added as participating centre to achieve target recruitment goal - Ability to perform the 68Ga-DOTATATE PET/CT at Amsterdam UMC location AMC - Possibility for participants to have study injections administered at home by trained nurses of a specialised homecare company (Eurocept Homecare).
31 August 2017	- Clearer definition of exclusion criterion concerning dopamine receptor agonist use: "Use of dopamine receptor agonists" was modified to "Use of dopamine receptor agonist in the past 6 months". Inclusions up to this amendment were not affected by the modification.
30 November 2018	- Increased sample size to 22 participants per treatment group to account for an observed overall dropout rate of ~25%. - More detailed statistical analysis section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/39070749

http://www.ncbi.nlm.nih.gov/pubmed/32792446

http://www.ncbi.nlm.nih.gov/pubmed/34191241