



## Clinical trial results:

**A single center, open label clinical trial investigating the long-term efficacy of rhLAMAN (recombinant human alpha-mannosidase or Lamazym) treatment in subjects with alpha-Mannosidosis who previously participated in Lamazym trials.**

### Summary

EudraCT number	2014-003950-15
Trial protocol	DK
Global end of trial date	13 June 2015

### Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

### Trial information

#### Trial identification

Sponsor protocol code	rhLAMAN-10
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02478840
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Zymenex A/S
Sponsor organisation address	Roskildevej 12C, Hilleroed, Denmark, 3400
Public contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., +39 0521 2791, clinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., +39 0521 2791, clinicaltrials_info@chiesi.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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	13 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2015
Global end of trial reached?	Yes
Global end of trial date	13 June 2015
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

The overall objective of the trial was the evaluation of the long-term efficacy of Lamazym treatment in patients with alpha-mannosidosis who were previously enrolled in trials with Lamazym and were currently receiving the treatment according to the AfterCare Program agreed with the National Authorities.

Primary objective: The primary objective of the trial was to evaluate the impact of the long-term treatment with Lamazym in patients with alpha-mannosidosis upon the level of biomarker oligosaccharides in serum and upon the endurance as measured by the change from Baseline in the number of steps climbed in 3 minutes (three minute stair climb test, 3MSCT).

To address the need for long-term data collection, the data collected during the present study was to be integrated with that from four previous studies (rhLAMAN-02, rhLAMAN-03, rhLAMAN-04 and rhLAMAN-05) and two ongoing studies (rhLAMAN-07 and rhLAMAN-09).

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements. Other than routine care, no specific measures for protection of trial subjects were implemented.

Background therapy:

There was no restriction on the use of concomitant medications/therapies during the trial. There are currently no known interactions of Lamazym with other medications.

Evidence for comparator: -

Actual start date of recruitment	16 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Denmark: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

Notes:

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**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)	9
Adolescents (12-17 years)	10
Adults (18-64 years)	14
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 34 patients (pts) were recruited with 35 pts identifiers; 1 patient participated in LAMAN-02/03 and later in LAMAN-05 and was counted once. Of the 34 pts, one patient received placebo in LAMAN 05 and then Lamazym in the AfterCare program. This patient discontinued shortly after starting the program and was excluded from all analyses.

### Pre-assignment

Screening details:

Of the 34 patients recruited, 1 (from the LAMAN05 study) discontinued the treatment shortly after starting the AfterCare program. As such, no data for this patient was collected during the active treatment, and so this patient was excluded from all analyses. Hence, 33 patients in total were actually analysed.

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study.

### Arms

Arm title	Lamazym 1mg/kg body weight
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Arm description:

Data displays were generally for patients overall. Each patient received the weekly dose of Lamazym of 1mg/kg.

Arm type	Experimental
Investigational medicinal product name	Lamazym
Investigational medicinal product code	
Other name	recombinant human lysosomal alpha-mannosidase
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

Lamazym, 1mg/kg body weight as intravenous infusion. Each patient received the weekly dose of Lamazym (as scheduled by their AfterCare program) in connection with an evaluation visit.

Number of subjects in period 1	Lamazym 1mg/kg body weight
Started	33
Completed	33

## Baseline characteristics

### Reporting groups

Reporting group title	Lamazym 1mg/kg body weight
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Reporting group description:

Data displays were generally for patients overall. Each patient received the weekly dose of Lamazym of 1mg/kg.

Reporting group values	Lamazym 1mg/kg body weight	Total	
Number of subjects	33	33	
Age categorical Units: Subjects			
Children (2-11 years)	9	9	
Adolescents (12-17 years)	10	10	
Adults (18-64 years)	14	14	
Age continuous Units: years			
arithmetic mean	17.1		
standard deviation	± 7.8	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	20	20	

### Subject analysis sets

Subject analysis set title	Overall - FAS
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Subject analysis set type	Full analysis
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Subject analysis set description:

Full Analysis Set (FAS): consisted of all patients who were dosed and whose efficacy was evaluated post-baseline. The end-point values for this Subject Analysis set reported are the changes from baseline to last observation.

Subject analysis set title	Overall - safety population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The safety analysis set (SAS) consisted of all patients who received at least one dose of trial medication.

Subject analysis set title	Baseline population
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Baseline values were defined as the last non-missing value before the first dose of Lamazym (derived from parental trials rhLAMAN-02 and rhLAMAN-05, respectively).

Subject analysis set title	Last observation population
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Last observation values were defined as the last available value at the end of rhLAMAN trials (derived from the last trial the patient participated in).

Reporting group values	Overall - FAS	Overall - safety population	Baseline population
Number of subjects	33	33	33
Age categorical Units: Subjects			
Children (2-11 years)	9	9	9
Adolescents (12-17 years)	10	10	10
Adults (18-64 years)	14	14	14
Age continuous Units: years			
arithmetic mean	17.1	17.1	17.1
standard deviation	± 7.8	± 7.8	± 7.8
Gender categorical Units: Subjects			
Female	13	13	13
Male	20	20	20

Reporting group values	Last observation population		
Number of subjects	33		
Age categorical Units: Subjects			
Children (2-11 years)	9		
Adolescents (12-17 years)	10		
Adults (18-64 years)	14		
Age continuous Units: years			
arithmetic mean	17.1		
standard deviation	± 7.8		
Gender categorical Units: Subjects			
Female	13		
Male	20		

## End points

### End points reporting groups

Reporting group title	Lamazym 1mg/kg body weight
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Reporting group description:

Data displays were generally for patients overall. Each patient received the weekly dose of Lamazym of 1mg/kg.

Subject analysis set title	Overall - FAS
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Subject analysis set type	Full analysis
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Subject analysis set description:

Full Analysis Set (FAS): consisted of all patients who were dosed and whose efficacy was evaluated post-baseline. The end-point values for this Subject Analysis set reported are the changes from baseline to last observation.

Subject analysis set title	Overall - safety population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

The safety analysis set (SAS) consisted of all patients who received at least one dose of trial medication.

Subject analysis set title	Baseline population
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Baseline values were defined as the last non-missing value before the first dose of Lamazym (derived from parental trials rhLAMAN-02 and rhLAMAN-05, respectively).

Subject analysis set title	Last observation population
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Last observation values were defined as the last available value at the end of rhLAMAN trials (derived from the last trial the patient participated in).

### Primary: Absolute change from baseline to last observation in serum oligosaccharides

End point title	Absolute change from baseline to last observation in serum oligosaccharides
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Primary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation.

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: $\mu\text{mol/L}$				
arithmetic mean (standard deviation)	-4.59 ( $\pm$ 3.23)	6.9 ( $\pm$ 2.3)	2.31 ( $\pm$ 2.19)	

<b>Attachments (see zip file)</b>	SERUM OLIGOSACCARIDES.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.74
upper limit	-3.45

## Primary: % change from baseline to last observation in serum oligosaccharides

End point title	% change from baseline to last observation in serum oligosaccharides
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Primary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: Percent				
arithmetic mean (standard deviation)	-62.8 (± 33.61)	6.9 (± 2.3)	2.31 (± 2.19)	

<b>Attachments (see zip file)</b>	SERUM OLIGOSACCARIDES.pdf
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## Statistical analyses



<b>Statistical analysis title</b>	Last observation vs baseline
Statistical analysis description: In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-74.7
upper limit	-50.8

### Primary: Absolute change from baseline to last observation in the 3MSCT

End point title	Absolute change from baseline to last observation in the 3MSCT
End point description: Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached	
End point type	Primary
End point timeframe: Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: steps/min				
arithmetic mean (standard deviation)	6.384 (± 10.54)	53.6 (± 12.53)	59.98 (± 16.29)	

<b>Attachments (see zip file)</b>	3MSCT.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
Statistical analysis description: In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.645
upper limit	10.12

### Primary: % change from baseline to last observation in the 3MSCT

End point title	% change from baseline to last observation in the 3MSCT
End point description:	
Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached	
End point type	Primary
End point timeframe:	
Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: steps/min				
arithmetic mean (standard deviation)	13.77 (± 25.83)	53.6 (± 12.53)	59.98 (± 16.29)	

<b>Attachments (see zip file)</b>	3MSCT.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
Statistical analysis description:	
In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.609
upper limit	22.92

### Secondary: Absolute change from baseline to last observation in the 6MSCT

End point title	Absolute change from baseline to last observation in the 6MSCT
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: meters				
arithmetic mean (standard deviation)	22.4 (± 63.2)	466.6 (± 90.1)	489 (± 85.7)	

Attachments (see zip file)	6MWT.pdf
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### Statistical analyses

Statistical analysis title	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
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Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	44.8

### Secondary: % change from baseline to last observation in the 6MSCT

End point title	% change from baseline to last observation in the 6MSCT
End point description:	
Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe:	
Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: meters				
arithmetic mean (standard deviation)	7.1 (± 22)	466.6 (± 90.1)	489 (± 85.7)	

<b>Attachments (see zip file)</b>	6MWT.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
Statistical analysis description:	
In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.071
Method	paired 2-sided T test

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	14.9

### Secondary: Absolute change from baseline to last observation in FVC (%)

End point title	Absolute change from baseline to last observation in FVC (%)
End point description:	
Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe:	
Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29 <sup>[1]</sup>	29 <sup>[2]</sup>	31 <sup>[3]</sup>	
Units: liters				
arithmetic mean (standard deviation)	8.1 (± 14.8)	84.9 (± 18.6)	93.1 (± 21.7)	

Notes:

[1] - This is the actual number of subjects on which the analysis was made

[2] - This is the actual number of subjects on which the analysis was made

[3] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	FVC %.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
Statistical analysis description:	
In a single-arm study, groups examined should not be added. The number N=60 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.4
upper limit	13.7

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**Secondary: % change from baseline to last observation in FVC (%)**

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End point title	% change from baseline to last observation in FVC (%)
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

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End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29 <sup>[4]</sup>	29 <sup>[5]</sup>	31 <sup>[6]</sup>	
Units: percent				
arithmetic mean (standard deviation)	10.5 (± 20.9)	84.9 (± 18.6)	93.1 (± 21.7)	

Notes:

[4] - This is the actual number of subjects on which the analysis was made

[5] - This is the actual number of subjects on which the analysis was made

[6] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	FVC %.pdf
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**Statistical analyses**

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<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=60 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.011
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	18.5

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**Secondary: Absolute change from baseline to last observation in FVC (L)**

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End point title	Absolute change from baseline to last observation in FVC (L)
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29 <sup>[7]</sup>	29 <sup>[8]</sup>	31 <sup>[9]</sup>	
Units: liters				
arithmetic mean (standard deviation)	0.578 (± 0.704)	2.651 (± 1.083)	3.233 (± 1.153)	

Notes:

[7] - This is the actual number of subjects on which the analysis was made

[8] - This is the actual number of subjects on which the analysis was made

[9] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	FVC L.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=60 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.845

## Secondary: % change from baseline to last observation in FVC (L)

End point title	% change from baseline to last observation in FVC (L)
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29 <sup>[10]</sup>	29 <sup>[11]</sup>	31 <sup>[12]</sup>	
Units: liters				
arithmetic mean (standard deviation)	28.38 (± 37.79)	2.651 (± 1.083)	3.233 (± 1.153)	

Notes:

[10] - This is the actual number of subjects on which the analysis was made

[11] - This is the actual number of subjects on which the analysis was made

[12] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	FVC L.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=60 (subject analysis set) is an innate error of the EudraCT database system

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.04
upper limit	42.76

### Secondary: Absolute change from baseline to last observation in predicted FEV1

End point title	Absolute change from baseline to last observation in predicted FEV1
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation



End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29 <sup>[13]</sup>	29 <sup>[14]</sup>	31 <sup>[15]</sup>	
Units: percent				
arithmetic mean (standard deviation)	3.7 (± 16.2)	83.8 (± 17.6)	88.3 (± 22.6)	

Notes:

[13] - This is the actual number of subjects on which the analysis was made

[14] - This is the actual number of subjects on which the analysis was made

[15] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	FEV %.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=60 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.226
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	9.9

## Secondary: % change from baseline to last observation in predicted FEV1

End point title	% change from baseline to last observation in predicted FEV1
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29 <sup>[16]</sup>	29 <sup>[17]</sup>	31 <sup>[18]</sup>	
Units: percent				
arithmetic mean (standard deviation)	5.1 (± 22.9)	83.8 (± 17.6)	88.3 (± 22.6)	

Notes:

[16] - This is the actual number of subjects on which the analysis was made

[17] - This is the actual number of subjects on which the analysis was made

[18] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	FEV %.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=60 (subject analysis set) is an innate error of the EudraCT database system

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.241
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	13.8

## Secondary: Absolute change from baseline to last observation in FEV1

End point title	Absolute change from baseline to last observation in FEV1
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

<b>End point values</b>	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29 <sup>[19]</sup>	29 <sup>[20]</sup>	31 <sup>[21]</sup>	
Units: Liters				
arithmetic mean (standard deviation)	0.399 (± 0.615)	2.441 (± 1)	2.864 (± 1.044)	

Notes:

[19] - This is the actual number of subjects on which the analysis was made

[20] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	FEV1 L.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=60 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.165
upper limit	0.633

## Secondary: % change from baseline to last observation in FEV1

End point title	% change from baseline to last observation in FEV1
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

<b>End point values</b>	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29 <sup>[22]</sup>	29 <sup>[23]</sup>	31 <sup>[24]</sup>	
Units: liters				
arithmetic mean (standard deviation)	21.31 (± 35.71)	2.441 (± 1)	2.864 (± 1.044)	

Notes:

[22] - This is the actual number of subjects on which the analysis was made

[23] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	FEV1 L.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=60 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.724
upper limit	34.889

## Secondary: Absolute change from baseline to last observation in PEF

End point title	Absolute change from baseline to last observation in PEF
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

<b>End point values</b>	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29 <sup>[25]</sup>	29 <sup>[26]</sup>	31 <sup>[27]</sup>	
Units: L/s				
arithmetic mean (standard deviation)	1.16 (± 1.733)	4.852 (± 2.044)	6.005 (± 2.371)	

Notes:

[25] - This is the actual number of subjects on which the analysis was made

[26] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	PEF.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=60 (subject analysis set) is an innate error of the EudraCT database system

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.501
upper limit	1.819

## Secondary: % change from baseline to last observation in PEF

End point title	% change from baseline to last observation in PEF
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

<b>End point values</b>	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	29 <sup>[28]</sup>	29 <sup>[29]</sup>	31 <sup>[30]</sup>	
Units: L/s				
arithmetic mean (standard deviation)	32.245 (± 56.081)	4.852 (± 2.044)	6.005 (± 2.371)	

Notes:

[28] - This is the actual number of subjects on which the analysis was made

[29] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	PEF.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=60 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.912
upper limit	53.577

## Secondary: Absolute change from baseline to last observation in BOT-2

End point title	Absolute change from baseline to last observation in BOT-2
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End point description:

BOT-2 total score is expressed as "point score".

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: score				
arithmetic mean (standard deviation)	5.1 (± 23.9)	107 (± 47.6)	112.1 (± 46)	

<b>Attachments (see zip file)</b>	BOT-2.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.23
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	13.6

## Secondary: % change from baseline to last observation in BOT-2

End point title	% change from baseline to last observation in BOT-2
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End point description:

BOT-2 total score is expressed as "point score".

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: score				
arithmetic mean (standard deviation)	13 (± 33.9)	107 (± 47.6)	112.1 (± 46)	

<b>Attachments (see zip file)</b>	BOT-2.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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**Statistical analysis description:**

In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.035
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	25

### Secondary: Absolute change from baseline to last observation in CSF oligosaccharides

End point title	Absolute change from baseline to last observation in CSF oligosaccharides
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**End point description:**

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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**End point timeframe:**

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: $\mu\text{Mol/L}$				
arithmetic mean (standard deviation)	-0.59 ( $\pm$ 1.97)	10.64 ( $\pm$ 3.53)	10.05 ( $\pm$ 3.31)	

<b>Attachments (see zip file)</b>	CSF_OLIGOSACCHARIDES.pdf
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**Statistical analyses**

<b>Statistical analysis title</b>	last observation vs baseline
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**Statistical analysis description:**

In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
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Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.094
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	0.11

### Secondary: % from baseline to last observation in CSF oligosaccharides

End point title	% from baseline to last observation in CSF oligosaccharides
End point description: Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe: Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation.	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: µMol/L				
arithmetic mean (standard deviation)	-3.54 (± 20.82)	10.64 (± 3.53)	10.05 (± 3.31)	

<b>Attachments (see zip file)</b>	CSF_OLIGOSACCHARIDES.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description: In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.336
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	3.84

### Secondary: Absolute change from baseline to last observation in TAU protein

End point title	Absolute change from baseline to last observation in TAU protein
End point description:	
Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe:	
Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: ng/L				
arithmetic mean (standard deviation)	20.8 (± 162.6)	655.6 (± 318.4)	676.4 (± 293.6)	

<b>Attachments (see zip file)</b>	CSF-Tau.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description:	
In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.468
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.9
upper limit	78.4

### Secondary: % change from baseline to last observation in TAU protein

End point title	% change from baseline to last observation in TAU protein
End point description:	
Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe:	
Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: ng/L				
arithmetic mean (standard deviation)	7.7 (± 26.7)	655.6 (± 318.4)	676.4 (± 293.6)	

<b>Attachments (see zip file)</b>	CSF-Tau.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
Statistical analysis description:	
In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.106
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	17.2

### Secondary: Absolute change from baseline to last observation in CSF-NFL

End point title	Absolute change from baseline to last observation in CSF-NFL
End point description:	
Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe:	
Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: ng/L				
arithmetic mean (standard deviation)	-26.2 (± 209.4)	430.3 (± 256.2)	-404.1 (± 136.7)	

<b>Attachments (see zip file)</b>	CSF-NFL.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
Statistical analysis description:	
In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.477
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-100
upper limit	48

### Secondary: % change from baseline to last observation in CSF-NFL

End point title	% change from baseline to last observation in CSF-NFL
End point description:	
Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe:	
Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: ng/L				
arithmetic mean (standard deviation)	11.6 (± 46.1)	430.3 (± 256.2)	404.1 (± 136.7)	

<b>Attachments (see zip file)</b>	CSF-NFL.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description:	
In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.158
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	28

### Secondary: Absolute change from baseline to last observation in CSF-GFA-P

End point title	Absolute change from baseline to last observation in CSF-GFA-P
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: ng/L				
arithmetic mean (standard deviation)	174.8 (± 498.8)	520.9 (± 379.1)	695.8 (± 420.9)	

<b>Attachments (see zip file)</b>	CSF-GFA-P.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
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Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.053
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	351.7

### Secondary: % change from baseline to last observation in CSF-GFA-P

End point title	% change from baseline to last observation in CSF-GFA-P
End point description:	
Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe:	
Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: ng/L				
arithmetic mean (standard deviation)	101.9 (± 147.6)	520.9 (± 379.1)	695.8 (± 420.9)	

<b>Attachments (see zip file)</b>	CSF-GFA-P.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description:	
In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	49.6
upper limit	154.3

### Secondary: Absolute change from baseline to last observation in serum immunoglobulin G

End point title	Absolute change from baseline to last observation in serum immunoglobulin G
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24 <sup>[31]</sup>	24 <sup>[32]</sup>	24 <sup>[33]</sup>	
Units: g/L				
arithmetic mean (standard deviation)	3.05 (± 1.56)	8.37 (± 4.2)	11.42 (± 4.59)	

Notes:

[31] - This is the actual number of subjects on which the analysis was made

[32] - This is the actual number of subjects on which the analysis was made

[33] - This is the actual number of subjects on which the analysis was made

Attachments (see zip file)	IGg.pdf
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### Statistical analyses

Statistical analysis title	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=48 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
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Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.39
upper limit	3.71

### Secondary: % change from baseline to last observation in serum Immunoglobulin G

End point title	% change from baseline to last observation in serum Immunoglobulin G
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24 <sup>[34]</sup>	24 <sup>[35]</sup>	24 <sup>[36]</sup>	
Units: g/L				
arithmetic mean (standard deviation)	44.07 (± 27.23)	8.37 (± 4.2)	11.42 (± 4.52)	

Notes:

[34] - This is the actual number of subjects on which the analysis

[35] - This is the actual number of subjects on which the analysis

[36] - This is the actual number of subjects on which the analysis

<b>Attachments (see zip file)</b>	IGg.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=48 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
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Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	32.58
upper limit	55.57

### Secondary: Absolute change from baseline to last observation in Leiter R Total Equivalent Age VR

End point title	Absolute change from baseline to last observation in Leiter R Total Equivalent Age VR
End point description:	Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.
End point type	Secondary
End point timeframe:	Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: years				
arithmetic mean (standard deviation)	0.265 (± 0.637)	5.879 (± 1.565)	6.144 (± 1.612)	

<b>Attachments (see zip file)</b>	Leiter Scale VR.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
Statistical analysis description:	In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.023
Method	paired 2-sided T test
Confidence interval	
sides	2-sided
lower limit	0.039
upper limit	0.491

## Secondary: % change from baseline to last observation in Leiter R Total Equivalent Age VR

End point title	% change from baseline to last observation in Leiter R Total Equivalent Age VR
End point description:	
Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe:	
Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: years				
arithmetic mean (standard deviation)	5.338 (± 10.45)	5.879 (± 1.565)	6.144 (± 1.612)	

<b>Attachments (see zip file)</b>	Leiter Scale VR.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description:	
In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006
Method	paired 2-sided T test

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.633
upper limit	9.043

## Secondary: Absolute change from baseline to last observation in Leiter R Total Equivalent Age AM

End point title	Absolute change from baseline to last observation in Leiter R Total Equivalent Age AM
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24 <sup>[37]</sup>	24 <sup>[38]</sup>	24 <sup>[39]</sup>	
Units: years				
arithmetic mean (standard deviation)	0.156 (± 1.519)	6.514 (± 2.176)	6.67 (± 1.757)	

Notes:

[37] - This is the actual number of subjects on which the analysis was made

[38] - This is the actual number of subjects on which the analysis was made

[39] - This is the actual number of subjects on which the analysis was made

Attachments (see zip file)	Leiter Scale AM.pdf
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## Statistical analyses

Statistical analysis title	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=48 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.619
Method	paired 2-sided T test

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.485
upper limit	0.798

## Secondary: % change from baseline to last observation in Leiter R Total Equivalent Age AM

End point title	% change from baseline to last observation in Leiter R Total Equivalent Age AM
End point description: Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe: Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24 <sup>[40]</sup>	24 <sup>[41]</sup>	24 <sup>[42]</sup>	
Units: years				
arithmetic mean (standard deviation)	9.345 (± 32.48)	6.514 (± 2.176)	6.67 (± 1.757)	

Notes:

[40] - This is the actual number of subjects on which the analysis was made

[41] - This is the actual number of subjects on which the analysis was made

[42] - This is the actual number of subjects on which the analysis was made

Attachments (see zip file)	Leiter Scale AM.pdf
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## Statistical analyses

Statistical analysis title	last observation vs baseline
Statistical analysis description: In a single-arm study, groups examined should not be added. The number N=48 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.172
Method	paired 2-sided T test

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.372
upper limit	23.063

## Secondary: Absolute change from baseline to last observation in bone conduction (best ear)

End point title	Absolute change from baseline to last observation in bone conduction (best ear)
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32 <sup>[43]</sup>	32 <sup>[44]</sup>	33 <sup>[45]</sup>	
Units: dbHL				
arithmetic mean (standard deviation)	-0.49 (± 6.58)	52.57 (± 12.36)	52.16 (± 13.13)	

Notes:

[43] - This is the actual number of subjects on which the analysis was made

[44] - This is the actual number of subjects on which the analysis was made

[45] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	Bone conduction best ear.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=65 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.674
Method	paired 2-sided T test

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.86
upper limit	1.88

### Secondary: % change from baseline to last observation in bone conduction (best ear)

End point title	% change from baseline to last observation in bone conduction (best ear)
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32 <sup>[46]</sup>	32 <sup>[47]</sup>	33 <sup>[48]</sup>	
Units: dbHL				
arithmetic mean (standard deviation)	-0.72 (± 14.54)	52.57 (± 12.36)	52.16 (± 13.13)	

Notes:

[46] - This is the actual number of subjects on which the analysis was made

[47] - This is the actual number of subjects on which the analysis was made

[48] - This is the actual number of subjects on which the analysis was made

Attachments (see zip file)	Bone conduction best ear.pdf
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### Statistical analyses

Statistical analysis title	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=65 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.782
Method	paired 2-sided T test

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.96
upper limit	4.52

## Secondary: Absolute change from baseline to last observation in bone conduction (left ear)

End point title	Absolute change from baseline to last observation in bone conduction (left ear)
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: dbHL				
arithmetic mean (standard deviation)	-2.83 (± 7.14)	62.34 (± 16.51)	59.51 (± 15.01)	

<b>Attachments (see zip file)</b>	Air conduction left ear.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.03
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.36
upper limit	-0.29



**Secondary: % change from baseline to last observation in bone conduction (left ear)**

End point title	% change from baseline to last observation in bone conduction (left ear)
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: dbHL				
arithmetic mean (standard deviation)	-3.79 ( $\pm$ 10.7)	62.34 ( $\pm$ 16.51)	59.51 ( $\pm$ 15.01)	

<b>Attachments (see zip file)</b>	Air conduction left ear.pdf
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**Statistical analyses**

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.58
upper limit	0

**Secondary: Absolute change from baseline to last observation in bone conduction (right ear)**

End point title	Absolute change from baseline to last observation in bone conduction (right ear)
End point description: Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe: Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: dbHL				
arithmetic mean (standard deviation)	-1.41 (± 10.31)	61.85 (± 17.9)	60.44 (± 15.7)	

<b>Attachments (see zip file)</b>	Air conduction right ear.pdf
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**Statistical analyses**

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description: In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.438
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.06
upper limit	2.25

**Secondary: % change from baseline to last observation in bone conduction (right ear)**

End point title	% change from baseline to last observation in bone conduction (right ear)
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: dbHL				
arithmetic mean (standard deviation)	0.54 ( $\pm$ 20.19)	61.85 ( $\pm$ 17.9)	60.44 ( $\pm$ 15.7)	

<b>Attachments (see zip file)</b>	Air conduction right ear.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.878
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.62
upper limit	7.7

### Secondary: Absolute change from baseline to last observation in CHAQ Disability Index

End point title	Absolute change from baseline to last observation in CHAQ Disability Index
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	33	33	33	
Units: integer				
arithmetic mean (standard deviation)	-0.13 (± 0.44)	1.36 (± 0.77)	1.23 (± 0.66)	

<b>Attachments (see zip file)</b>	CHAQ Disability Index.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.095
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.29
upper limit	0.02

### Secondary: % change from baseline to last observation in CHAQ Disability Index

End point title	% change from baseline to last observation in CHAQ Disability Index
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	31 <sup>[49]</sup>	33 <sup>[50]</sup>	33 <sup>[51]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-2.41 (± 45.03)	1.36 (± 0.77)	1.23 (± 0.66)	

Notes:

[49] - This is the actual number of subjects on which the analysis was made

[50] - This is the actual number of subjects on which the analysis was made

[51] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	CHAQ Disability Index.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=66 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.768
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.9
upper limit	14.11

## Secondary: Absolute change from baseline to last observation in CHAQ VAS pain

End point title	Absolute change from baseline to last observation in CHAQ VAS pain
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32 <sup>[52]</sup>	32	33	
Units: integer				
arithmetic mean (standard deviation)	-0.173 (± 0.647)	0.618 (± 0.731)	0.431 (± 0.616)	

Notes:

[52] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	CHAQ VAS PAIN.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=65 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.139
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.407
upper limit	0.06

## Secondary: % change from baseline to last observation in CHAQ VAS pain

End point title	% change from baseline to last observation in CHAQ VAS pain
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21 <sup>[53]</sup>	32 <sup>[54]</sup>	33 <sup>[55]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-17 (± 109.8)	0.618 (±	0.431 (±	

Notes:

[53] - This is the actual number of subjects on which the analysis was made

[54] - This is the actual number of subjects on which the analysis was made

[55] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	CHAQ VAS PAIN.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=65 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.485
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67
upper limit	32.94

## Secondary: Absolute change from baseline to last observation in CHAQ VAS general

End point title	Absolute change from baseline to last observation in CHAQ VAS general
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

<b>End point values</b>	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32 <sup>[56]</sup>	32 <sup>[57]</sup>	33 <sup>[58]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-0.068 (± 0.621)	1.049 (± 0.77)	0.952 (± 0.723)	

Notes:

[56] - This is the actual number of subjects on which the analysis was made

[57] - This is the actual number of subjects on which the analysis was made

[58] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	CHAQ General VAS.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=65 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.543
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.291
upper limit	0.156

## Secondary: % change from baseline to last observation in CHAQ VAS general

End point title	% change from baseline to last observation in CHAQ VAS general
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

<b>End point values</b>	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27 <sup>[59]</sup>	32 <sup>[60]</sup>	33 <sup>[61]</sup>	
Units: integer				
arithmetic mean (standard deviation)	10.36 (± 73.63)	1.049 (± 0.77)	0.952 (± 0.723)	



Notes:

[59] - This is the actual number of subjects on which the analysis was made

[60] - This is the actual number of subjects on which the analysis was made

[61] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	CHAQ General VAS.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=65 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.471
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.8
upper limit	39.48

## Secondary: Absolute change from baseline to last observation in EQ-5D-5L Health Index

End point title	Absolute change from baseline to last observation in EQ-5D-5L Health Index
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24 <sup>[62]</sup>	24 <sup>[63]</sup>	24 <sup>[64]</sup>	
Units: integer				
arithmetic mean (standard deviation)	0.05 (± 0.135)	0.622 (± 0.17)	0.672 (± 0.167)	

Notes:

[62] - This is the actual number of subjects on which the analysis was made

[63] - This is the actual number of subjects on which the analysis was made

[64] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	EQ-5D-L.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	Last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=48 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.08
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0066
upper limit	0.1075

## Secondary: % change from baseline to last observation in EQ-5D-5L Health Index

End point title	% change from baseline to last observation in EQ-5D-5L Health Index
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

<b>End point values</b>	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	24 <sup>[65]</sup>	24 <sup>[66]</sup>	24 <sup>[67]</sup>	
Units: integer				
arithmetic mean (standard deviation)	11.23 (± 24.72)	0.622 (± 0.17)	0.672 (± 0.167)	

Notes:

[65] - This is the actual number of subjects on which the analysis was made

[66] - This is the actual number of subjects on which the analysis was made

[67] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	EQ-5D-L.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=48 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0036
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	21.6682

## Secondary: absolute change from baseline to last observation in MRI ADC grey

End point title	absolute change from baseline to last observation in MRI ADC grey
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

<b>End point values</b>	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 <sup>[68]</sup>	9 <sup>[69]</sup>	9 <sup>[70]</sup>	
Units: 10 <sup>-6</sup> mm <sup>2</sup> /s				
arithmetic mean (standard deviation)	160.2 (± 68.4)	796.9 (± 37.1)	957.1 (± 65.8)	

Notes:

[68] - This is the actual number of subjects on which the analysis was made

[69] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	MRI ADC Grey.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	107.7
upper limit	212.8

## Secondary: % change from baseline to last observation in MRI ADC grey

End point title	% change from baseline to last observation in MRI ADC grey
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

<b>End point values</b>	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 <sup>[71]</sup>	9 <sup>[72]</sup>	9 <sup>[73]</sup>	
Units: 10 <sup>-6</sup> mm <sup>2</sup> /s				
arithmetic mean (standard deviation)	20.3 (± 8.8)	796.8 (± 37.1)	957.1 (± 65.8)	

Notes:

[71] - This is the actual number of subjects on which the analysis was made

[72] - This is the actual number of subjects on which the analysis was made

[73] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	MRI ADC Grey.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.5
upper limit	27

### Secondary: absolute change from baseline to last observation in MRI ADC standard

End point title	absolute change from baseline to last observation in MRI ADC standard
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

<b>End point values</b>	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 <sup>[74]</sup>	9 <sup>[75]</sup>	9 <sup>[76]</sup>	
Units: 10 <sup>-6</sup> mm <sup>2</sup> /s				
arithmetic mean (standard deviation)	-5.7 (± 42.4)	856.1 (± 91.7)	850.4 (± 63.4)	

Notes:

[74] - This is the actual number of subjects on which the analysis was made

[75] - This is the actual number of subjects on which the analysis was made

[76] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	MRI ADC Standard.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.699
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.3
upper limit	27

### Secondary: % change from baseline to last observation in MRI ADC standard

End point title	% change from baseline to last observation in MRI ADC standard
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 <sup>[77]</sup>	9 <sup>[78]</sup>	9 <sup>[79]</sup>	
Units: 10 <sup>-6</sup> mm <sup>2</sup> /s				
arithmetic mean (standard deviation)	-0.3 (± 4.5)	856.1 (± 91.7)	850.4 (± 63.4)	

Notes:

[77] - This is the actual number of subjects on which the analysis was made

[78] - This is the actual number of subjects on which the analysis was made

[79] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	MRI ADC Standard.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.83
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	3.2

### Secondary: absolute change from baseline to last observation in MRI ADC white

End point title	absolute change from baseline to last observation in MRI ADC white
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 <sup>[80]</sup>	9 <sup>[81]</sup>	9 <sup>[82]</sup>	
Units: 10 <sup>-6</sup> mm <sup>2</sup> /s				
arithmetic mean (standard deviation)	-113 (± 93.5)	913 (± 119.5)	800.3 (± 47.3)	

Notes:

[80] - This is the actual number of subjects on which the analysis was made

[81] - This is the actual number of subjects on which the analysis was made

[82] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	MRI ADC White.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description: In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-185
upper limit	-40.8

### Secondary: % change from baseline to last observation in MRI ADC white

End point title	% change from baseline to last observation in MRI ADC white
End point description: Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe: Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

<b>End point values</b>	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 <sup>[83]</sup>	9 <sup>[84]</sup>	9 <sup>[85]</sup>	
Units: 10 <sup>-6</sup> mm <sup>2</sup> /s				
arithmetic mean (standard deviation)	-11.5 (± 8.3)	913 (± 119.5)	800.3 (± 47.3)	

Notes:

[83] - This is the actual number of subjects on which the analysis was made

[84] - This is the actual number of subjects on which the analysis was made

[85] - This is the actual number of subjects on which the analysis was made



<b>Attachments (see zip file)</b>	MRI ADC White.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	-5.1

## Secondary: absolute change from baseline to last observation in MRS mannose complex visual Grey

End point title	absolute change from baseline to last observation in MRS mannose complex visual Grey
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 <sup>[86]</sup>	9 <sup>[87]</sup>	9 <sup>[88]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-0.4 (± 0.5)	1.9 (± 0.8)	1.4 (± 1.1)	

Notes:

[86] - This is the actual number of subjects on which the analysis was made

[87] - This is the actual number of subjects on which the analysis was made

[88] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	Mannose Complex Visual Grey.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description: In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.035
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0

### Secondary: % change from baseline to last observation in MRS mannose complex visual Grey

End point title	% change from baseline to last observation in MRS mannose complex visual Grey
End point description: Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe: Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 <sup>[89]</sup>	9 <sup>[90]</sup>	9 <sup>[91]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-33.3 (± 43.3)	1.9 (± 0.8)	1.4 (± 1.1)	

Notes:

[89] - This is the actual number of subjects on which the analysis was made

[90] - This is the actual number of subjects on which the analysis was made

[91] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	Mannose Complex Visual Grey.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description: In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set)	

is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.05
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-66.6
upper limit	0

## Secondary: absolute change from baseline to last observation in MRS mannose complex visual Standard

End point title	absolute change from baseline to last observation in MRS mannose complex visual Standard
End point description: Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe: Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8 <sup>[92]</sup>	8 <sup>[93]</sup>	9 <sup>[94]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-0.1 (± 0.6)	1.6 (± 1.2)	1.3 (± 1.3)	

Notes:

[92] - This is the actual number of subjects on which the analysis was made

[93] - This is the actual number of subjects on which the analysis was made

[94] - This is the actual number of subjects on which the analysis was made

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## Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description: In a single-arm study, groups examined should not be added. The number N=17 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.598
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.4

### Secondary: % change from baseline to last observation in MRS mannose complex visual Standard

End point title	% change from baseline to last observation in MRS mannose complex visual Standard
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	6 <sup>[95]</sup>	8 <sup>[96]</sup>	9 <sup>[97]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-8.3 (± 37.6)	1.6 (± 1.2)	1.3 (± 1.3)	

Notes:

[95] - This is the actual number of subjects on which the analysis was made

[96] - This is the actual number of subjects on which the analysis was made

[97] - This is the actual number of subjects on which the analysis was made

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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=17 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
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Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.611
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.8
upper limit	31.2

### Secondary: absolute change from baseline to last observation in MRS mannose complex visual White

End point title	absolute change from baseline to last observation in MRS mannose complex visual White
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 <sup>[98]</sup>	9 <sup>[99]</sup>	9 <sup>[100]</sup>	
Units: integer				
arithmetic mean (standard deviation)	0 (± 0.9)	1.8 (± 1.2)	1.8 (± 0.8)	

Notes:

[98] - This is the actual number of subjects on which the analysis was made

[99] - This is the actual number of subjects on which the analysis was made

[100] - This is the actual number of subjects on which the analysis was made

Attachments (see zip file)	MRI ADC White.pdf
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### Statistical analyses

Statistical analysis title	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Last observation population v Baseline population
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Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.7

### Secondary: % change from baseline to last observation in MRS mannose complex visual White

End point title	% change from baseline to last observation in MRS mannose complex visual White
End point description:	Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached
End point type	Secondary
End point timeframe:	Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7 <sup>[101]</sup>	9 <sup>[102]</sup>	9 <sup>[103]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-4.8 (± 51.6)	1.8 (± 1.2)	1.8 (± 0.8)	

Notes:

[101] - This is the actual number of subjects on which the analysis was made

[102] - This is the actual number of subjects on which the analysis was made

[103] - This is the actual number of subjects on which the analysis was made

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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description:	In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set) is an innate error of the EudraCT database system.
Comparison groups	Last observation population v Baseline population

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.815
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.4
upper limit	42.9

### Secondary: absolute change from baseline to last observation in MRS numerical mannose complex index grey

End point title	absolute change from baseline to last observation in MRS numerical mannose complex index grey
End point description:	Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached
End point type	Secondary
End point timeframe:	Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 <sup>[104]</sup>	9 <sup>[105]</sup>	9 <sup>[106]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-0.2 (± 0.4)	1 (± 0.5)	0.9 (± 0.3)	

Notes:

[104] - This is the actual number of subjects on which the analysis was made

[105] - This is the actual number of subjects on which the analysis was made

[106] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	Numerical Mannose Complex Index. Grey.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description:	In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set) is an innate error of the EudraCT database system.
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.329
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.2

### Secondary: % change from baseline to last observation in MRS numerical mannose complex index grey

End point title	% change from baseline to last observation in MRS numerical mannose complex index grey
End point description:	
Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached	
End point type	Secondary
End point timeframe:	
Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	9 <sup>[107]</sup>	9 <sup>[108]</sup>	9 <sup>[109]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-4.5 (± 34.1)	1 (± 0.5)	0.9 (± 0.3)	

Notes:

[107] - This is the actual number of subjects on which the analysis was made

[108] - This is the actual number of subjects on which the analysis was made

[109] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	Numerical Mannose Complex Index. Grey.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description:	
In a single-arm study, groups examined should not be added. The number N=18 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population



Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.705
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.7
upper limit	21.7

### Secondary: absolute change from baseline to last observation in MRS numerical mannose complex index standard

End point title	absolute change from baseline to last observation in MRS numerical mannose complex index standard
End point description: Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached	
End point type	Secondary
End point timeframe: Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7 <sup>[110]</sup>	7 <sup>[111]</sup>	9 <sup>[112]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-0.1 (± 0.4)	1 (± 0.3)	0.9 (± 0.4)	

Notes:

[110] - This is the actual number of subjects on which the analysis was made

[111] - This is the actual number of subjects on which the analysis was made

[112] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	Numerical Mannose Complex Index Standard.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description: In a single-arm study, groups examined should not be added. The number N=16 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.704
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.3

### Secondary: % change from baseline to last observation in MRS numerical mannose complex index standard

End point title	% change from baseline to last observation in MRS numerical mannose complex index standard
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End point description:

Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached

End point type	Secondary
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End point timeframe:

Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7 <sup>[113]</sup>	7 <sup>[114]</sup>	9 <sup>[115]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-7.7 (± 28.6)	1 (± 0.3)	0.9 (± 0.4)	

Notes:

[113] - This is the actual number of subjects on which the analysis was made

[114] - This is the actual number of subjects on which the analysis was made

[115] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	Numerical Mannose Complex Index Standard.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
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Statistical analysis description:

In a single-arm study, groups examined should not be added. The number N=16 (subject analysis set) is an innate error of the EudraCT database system.

Comparison groups	Baseline population v Last observation population
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Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.504
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.2
upper limit	18.8

### Secondary: absolute change from baseline to last observation in MRS numerical mannose complex index white

End point title	absolute change from baseline to last observation in MRS numerical mannose complex index white
End point description:	
Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.	
End point type	Secondary
End point timeframe:	
Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation	

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8 <sup>[116]</sup>	8 <sup>[117]</sup>	9 <sup>[118]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-0.1 (± 0.3)	1 (± 0.4)	0.8 (± 0.2)	

Notes:

[116] - This is the actual number of subjects on which the analysis was made

[117] - This is the actual number of subjects on which the analysis was made

[118] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	Numerical Mannose Complex Index White.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description:	
In a single-arm study, groups examined should not be added. The number N=17 (subject analysis set) is an innate error of the EudraCT database system.	
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.287
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.1

## Secondary: % change from baseline to last observation in MRS numerical mannose complex index white

End point title	% change from baseline to last observation in MRS numerical mannose complex index white
End point description:	Only (absolute and percent) changes from baseline to last observation are inserted in the system. For the complete data regarding the other Timepoints see the pdf attached.
End point type	Secondary
End point timeframe:	Timepoints: Month 6, Month 12, Month 18, Month 24, Month 36, Month 48 and Last Observation

End point values	Overall - FAS	Baseline population	Last observation population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	8 <sup>[119]</sup>	8 <sup>[120]</sup>	9 <sup>[121]</sup>	
Units: integer				
arithmetic mean (standard deviation)	-2.9 (± 33.7)	1 (± 0.4)	0.8 (± 0.2)	

Notes:

[119] - This is the actual number of subjects on which the analysis was made

[120] - This is the actual number of subjects on which the analysis was made

[121] - This is the actual number of subjects on which the analysis was made

<b>Attachments (see zip file)</b>	Numerical Mannose Complex Index White.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	last observation vs baseline
Statistical analysis description:	In a single-arm study, groups examined should not be added. The number N=17 (subject analysis set) is an innate error of the EudraCT database system.
Comparison groups	Baseline population v Last observation population

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.813
Method	paired 2-sided T test
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.1
upper limit	25.3

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose to last observation.

Adverse event reporting additional description:

A total of 546 TEAEs were reported in 29 patients. Approx. one third of patients (12 patients) experienced serious TEAEs. Only 3 patients experienced TEAEs that were severe in intensity. There were no deaths, and no TEAEs led to treatment discontinuation.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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### Reporting groups

Reporting group title	Overall population-safety
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Reporting group description:

The safety analysis set (SAS) consisted of all patients who received at least one dose of trial medication.

Serious adverse events	Overall population-safety		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 33 (36.36%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Knee deformity			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sjogren-Larsson syndrome			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Vascular disorders			
Syncope			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Malabsorption from administration site			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint swelling			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Device related infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ear infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	Overall population-safety		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 33 (87.88%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Surgical and medical procedures			
Catheter removal			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Ear tube insertion			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Tooth extraction			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
General disorders and administration site conditions			



Chills			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	9		
Fatigue			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Malaise			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	11 / 33 (33.33%)		
occurrences (all)	26		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	9 / 33 (27.27%)		
occurrences (all)	12		
Rhinorrhoea			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Investigations			
Weight increased			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	7		
Injury, poisoning and procedural complications			
Arthropod bite			

subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Contusion			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	10		
Excoriation			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	18		
Ligament sprain			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Post lumbar puncture syndrome			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Wound			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	10		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	13 / 33 (39.39%)		
occurrences (all)	27		
Loss of consciousness			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Syncope			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Eye disorders			

Conjunctival hyperaemia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Eye infection subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Eye pruritus subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 5		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3		
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4		
Diarrhoea subjects affected / exposed occurrences (all)	9 / 33 (27.27%) 11		
Nausea subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3		
Reflux gastritis subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Toothache subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 3		
Vomiting subjects affected / exposed occurrences (all)	10 / 33 (30.30%) 14		
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Erythema			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Scar pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 33 (12.12%)</p> <p>5</p> <p>5 / 33 (15.15%)</p> <p>5</p> <p>2 / 33 (6.06%)</p> <p>2</p>		
<p>Renal and urinary disorders</p> <p>Pollakiuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 33 (6.06%)</p> <p>2</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Myalgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 33 (21.21%)</p> <p>14</p> <p>5 / 33 (15.15%)</p> <p>5</p> <p>2 / 33 (6.06%)</p> <p>3</p> <p>6 / 33 (18.18%)</p> <p>14</p>		
<p>Infections and infestations</p> <p>Acute tonsillitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Ear infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gastroenteritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Influenza</p>	<p>2 / 33 (6.06%)</p> <p>2</p> <p>6 / 33 (18.18%)</p> <p>7</p> <p>6 / 33 (18.18%)</p> <p>7</p>		

subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Laryngitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	23 / 33 (69.70%)		
occurrences (all)	89		
Urinary tract infection			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Otitis media			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

There are no limitations or caveats to this summary of results
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Notes: