



Clinical trial results:

A single-centre, open single-arm study where the safety, tolerability and efficacy of subcutaneously administered ILB will be evaluated in patients with Amyotrophic Lateral Sclerosis

Summary

EudraCT number	2017-005065-47
Trial protocol	SE
Global end of trial date	20 August 2019

Results information

Result version number	v1
This version publication date	05 September 2020
First version publication date	05 September 2020

Trial information

Trial identification

Sponsor protocol code	TM-105
-----------------------	--------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03613571
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TikoMed AB
Sponsor organisation address	Box 81, Viken, Sweden, 26303
Public contact	Lars Bruce, TikoMed AB, +46 707238414, florence.lange@tikomed.com
Scientific contact	Lars Bruce, TikoMed AB, +46 707238414, florence.lange@tikomed.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 August 2019
Global end of trial reached?	Yes
Global end of trial date	20 August 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To study safety and tolerability of subcutaneously administered ILB in patients diagnosed with ALS.

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki that are consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements. Informed consent was obtained from all patients prior to initiation of the study. Protocol deviations related to GCP that were reported during the study are discussed further in the section "More information".

Background therapy:

No background therapy was used in the trial.

Evidence for comparator:

There was no comparator used in this study. There was 1 treatment group that received the test product.

Actual start date of recruitment	17 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	9

From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Screening was performed 30 days prior to treatment. The first patient screened was on 2018-09-17. It was planned to include 15 patients in the study, however due to delays in recruitment and the fact that no safety concerns were reported, it was decided by the Sponsor to terminate patient recruitment and conclude the study with 13 patients

Pre-assignment

Screening details:

Twenty patients were screened 13 were included and treated. The reasons for screening failure were: not fulfilment of inclusion/exclusion criteria and death before study start. All 13 patients were included in the analysis. One patient did not attend the last follow-up visit due to ALS progression. A total of 12 patients completed the study.

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:

Not applicable (open-label study)

Arms

Arm title	ILB treatment group
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	ILB
Investigational medicinal product code	
Other name	The active pharmaceutical ingredient is a low molecular weight dextran sulfate (LMW-DS, approx. 20 % sulfate, mean MW 5 kDa)
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

There was only 1 treatment group in the study (ILB treatment group). The dose administered (1 mg/kg) depended on the patient's body weight at Visit 2, prior to the first ILB administration.

The ILB was administered in single short term subcutaneous injections on alternative sides of the abdomen, thigh or buttock, in that order of priority. The maximum volume injected at each injection site was approximately 2 mL and the number of injections per patient could range between 1 and 3 sites depending on the volume to be injected. Each administration occurred within ± 3 days from the pre-defined dosing days (Days 1, 8, 15, 22 and 29) with at least 4 days between 2 IMP administrations. ILB administration was performed by the study personnel and patients were observed for at least 3 hours after the injection.

Number of subjects in period 1	ILB treatment group
Started	13
Treated with ILB	13
Completed	13

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	13	13	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	4	4	
85 years and over	0	0	
Not recorded	0	0	
Age continuous			
Units: years			
arithmetic mean	56.5		
standard deviation	± 13.3	-	
Gender categorical			
Units: Subjects			
Female	3	3	
Male	10	10	
Ethnic group			
Units: Subjects			
Not Hispanic or latino	13	13	
Race			
Units: Subjects			
White	13	13	
Body Mass Index			
Units: kg/m2			
arithmetic mean	25.2		
standard deviation	± 2.9	-	
Height			
Units: cm			
arithmetic mean	178.7		
standard deviation	± 11	-	
Weight			
Units: kg			
arithmetic mean	80.6		
standard deviation	± 11.6	-	

Subject analysis sets

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set was defined as patients who received any dose of the test product (ILB)	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description: Defined as all patients who received at least 1 dose of the test product (ILB) and with at least 1 efficacy measurement	
Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol
Subject analysis set description: Defined as all patients who received at least 1 dose of the test product (ILB) and with at least 1 efficacy measurement. This analysis set was the same as the full analysis set.	
Subject analysis set title	Results at baseline
Subject analysis set type	Sub-group analysis
Subject analysis set description: This sub-group consists of the same subjects as the safety analysis set and the full analysis set. The sub-group was created to present the statistical analysis of changes from baseline in this single-arm study. The total number of subjects in the analysis is 13.	
Subject analysis set title	Results at post-treatment visits
Subject analysis set type	Sub-group analysis
Subject analysis set description: This sub-group consists of the same subjects as the safety analysis set and the full analysis set. The sub-group was created to present the statistical analysis of changes from baseline in this single-arm study. The total number of subjects in the analysis is 13.	
Subject analysis set title	TEAEs during the treatment period
Subject analysis set type	Sub-group analysis
Subject analysis set description: TEAEs that occurred during the treatment period are reported using this group. This group consisted of the same subjects as in the Safety analysis set (N=13).	
Subject analysis set title	TEAEs during the follow-up period
Subject analysis set type	Sub-group analysis
Subject analysis set description: TEAEs that occurred during the follow-up period are reported using this group. This group consisted of the same subjects as in the Safety analysis set (N=13).	
Subject analysis set title	Safety analysis set - copy
Subject analysis set type	Sub-group analysis
Subject analysis set description: This is not a separate subgroup of subjects but contains data for the same 13 subjects as in the safety analysis set.	

Reporting group values	Safety analysis set	Full analysis set	Per protocol analysis set
Number of subjects	13	13	13
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0

Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	9	9
From 65-84 years	4	4	4
85 years and over	0	0	0
Not recorded	0	0	0
Age continuous Units: years			
arithmetic mean	56.5	56.5	56.5
standard deviation	± 13.3	± 13.3	± 13.3
Gender categorical Units: Subjects			
Female	3	3	3
Male	10	10	10
Ethnic group Units: Subjects			
Not Hispanic or latino	13	13	13
Race Units: Subjects			
White	13	13	13
Body Mass Index Units: kg/m2			
arithmetic mean	25.2	25.2	25.2
standard deviation	± 2.9	± 2.9	± 2.9
Height Units: cm			
arithmetic mean	178.7	178.7	178.7
standard deviation	± 11	± 11	± 11
Weight Units: kg			
arithmetic mean	80.6	80.6	80.6
standard deviation	± 11.6	± 11.6	± 11.6

Reporting group values	Results at baseline	Results at post-treatment visits	TEAEs during the treatment period
Number of subjects	13	13	13
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Not recorded			
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	±

Gender categorical Units: Subjects			
Female			
Male			
Ethnic group Units: Subjects			
Not Hispanic or latino			
Race Units: Subjects			
White			
Body Mass Index Units: kg/m2 arithmetic mean standard deviation	\pm	\pm	\pm
Height Units: cm arithmetic mean standard deviation	\pm	\pm	\pm
Weight Units: kg arithmetic mean standard deviation	\pm	\pm	\pm

Reporting group values	TEAEs during the follow-up period	Safety analysis set - copy	
Number of subjects	13	13	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over Not recorded			
Age continuous Units: years arithmetic mean standard deviation	\pm	\pm	
Gender categorical Units: Subjects			
Female			
Male			
Ethnic group Units: Subjects			
Not Hispanic or latino			
Race Units: Subjects			

White			
-------	--	--	--

Body Mass Index Units: kg/m2 arithmetic mean standard deviation	±	±	
Height Units: cm arithmetic mean standard deviation	±	±	
Weight Units: kg arithmetic mean standard deviation	±	±	

End points

End points reporting groups

Reporting group title	ILB treatment group
Reporting group description: -	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set was defined as patients who received any dose of the test product (ILB)	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Defined as all patients who received at least 1 dose of the test product (ILB) and with at least 1 efficacy measurement	
Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
Defined as all patients who received at least 1 dose of the test product (ILB) and with at least 1 efficacy measurement. This analysis set was the same as the full analysis set.	
Subject analysis set title	Results at baseline
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This sub-group consists of the same subjects as the safety analysis set and the full analysis set. The sub-group was created to present the statistical analysis of changes from baseline in this single-arm study. The total number of subjects in the analysis is 13.	
Subject analysis set title	Results at post-treatment visits
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This sub-group consists of the same subjects as the safety analysis set and the full analysis set. The sub-group was created to present the statistical analysis of changes from baseline in this single-arm study. The total number of subjects in the analysis is 13.	
Subject analysis set title	TEAEs during the treatment period
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
TEAEs that occurred during the treatment period are reported using this group. This group consisted of the same subjects as in the Safety analysis set (N=13).	
Subject analysis set title	TEAEs during the follow-up period
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
TEAEs that occurred during the follow-up period are reported using this group. This group consisted of the same subjects as in the Safety analysis set (N=13).	
Subject analysis set title	Safety analysis set - copy
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This is not a separate subgroup of subjects but contains data for the same 13 subjects as in the safety analysis set.	

Primary: Frequency, seriousness and intensity of Treatment-emergent Adverse Events

End point title	Frequency, seriousness and intensity of Treatment-emergent Adverse Events ^[1]
End point description:	
A Treatment-emergent Adverse Event (TEAE) was defined as any AE not present prior to the initiation of IMP administration or any event already present that worsened in either intensity or frequency following	

exposure to the IMP. A serious AE (SAE) was defined as any untoward medical occurrence that at any dose:

- Resulted in death
- Was life-threatening
- Required inpatient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity, or
- Was a congenital anomaly/birth defect

All AEs and SAEs were recorded from start of IMP administration until the end of follow-up (Visit 9). Adverse events that occurred before first IMP treatment were reported separately as baseline events.

End point type	Primary
End point timeframe:	
Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary endpoint "Frequency, seriousness and intensity of Treatment-emergent Adverse Events" was only analyzed descriptively in this study. No statistical analyses were performed.

End point values	ILB treatment group	Safety analysis set	TEAEs during the treatment period	TEAEs during the follow-up period
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	13	13	13 ^[2]
Units: subjects				
TEAE	11	11	9	6
SAE	0	0	0	0
TEAE leading to withdrawal	0	0	0	0
TEAE leading to death	0	0	0	0
Causality (possibly related)	3	3	2	1
Causality (unrelated)	11	11	8	6
Severity (Mild)	10	10	8	4
Severity (Moderate)	4	4	1	4
Severity (Severe)	0	0	0	0

Notes:

[2] - This is not a separate analysis set but reports data for the same 13 subjects as during treatment.

Statistical analyses

No statistical analyses for this end point

Primary: Physical examination

End point title	Physical examination ^[3]
End point description:	
A complete physical examination included assessments of the head, eyes, ears, nose, throat, cardiac, peripheral vascular, pulmonary, musculoskeletal, neurologic, abdominal, lymphatic and dermatologic functions. Abnormal findings were specified and presented by patient and summarised in frequency tables. No statistical analysis was performed.	
End point type	Primary
End point timeframe:	
Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary endpoint "Physical examination" was only analyzed descriptively in this study. No statistical analyses were performed.

End point values	ILB treatment group	Safety analysis set	Safety analysis set - copy	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[4]	
Units: subjects				
Clinically significant abnormal findings	2	2	2	

Notes:

[4] - This is not a separate analysis set but contains the same 13 subjects as the safety analysis set.

Statistical analyses

No statistical analyses for this end point

Primary: Vital signs-blood pressure

End point title	Vital signs-blood pressure
-----------------	----------------------------

End point description:

Diastolic and systolic blood pressure was measured in supine position after 5 minutes of rest using the same method each time. Data were presented by visit for each parameter and patient and summarised using summary statistics, including absolute and percent change from baseline. The baseline was defined as the last measurement prior to first dose of the test product (i.e. measurement at Visit 2).

End point type	Primary
----------------	---------

End point timeframe:

Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)

End point values	Safety analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[5]	
Units: mmHg				
arithmetic mean (standard deviation)				
Diastolic pressure at baseline (Visit 2)	79.4 (± 9.2)	79.4 (± 9.2)	79.4 (± 9.2)	
Systolic pressure at baseline (Visit 2)	139.4 (± 14.4)	139.4 (± 14.4)	139.4 (± 14.4)	
Max relative decrease (%) in diastolic pressure	4.2 (± 6.6)	4.2 (± 6.6)	4.2 (± 6.6)	
Max relative decrease (%) in systolic pressure	5.1 (± 7.4)	5.1 (± 7.4)	5.1 (± 7.4)	

Notes:

[5] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Statistical analyses

Statistical analysis title	No change in blood pressure
----------------------------	-----------------------------

Statistical analysis description:

The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this

report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the safety analysis set to assess the statistical significance of changes from baseline.

Comparison groups	Results at baseline v Results at post-treatment visits
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	> 0.05 ^[7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[7] - There was no statistically significant change in blood pressure during the study.

Primary: Vital signs- heart rate

End point title	Vital signs- heart rate
-----------------	-------------------------

End point description:

Heart rate was measured in supine position after 5 minutes of rest using the same method each time. Data were presented by visit for each parameter and patient and summarised using summary statistics, including absolute and percent change from baseline. The baseline was defined as the last measurement prior to first dose of the test product (i.e. measurement at Visit 2).

End point type	Primary
----------------	---------

End point timeframe:

Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)

End point values	Safety analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[8]	
Units: beats/min				
arithmetic mean (standard deviation)				
Heart rate at baseline (Visit 2)	70.1 (± 10.0)	70.1 (± 10.0)	70.1 (± 10.0)	
Max relative decrease (%) in heart rate	3.8 (± 8.6)	3.8 (± 8.6)	3.8 (± 8.6)	
Max relative increase (%) in heart rate	3.2 (± 11.4)	3.2 (± 11.4)	3.2 (± 11.4)	

Notes:

[8] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Statistical analyses

Statistical analysis title	No change in heart rate
----------------------------	-------------------------

Statistical analysis description:

The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the safety analysis set to assess the statistical significance of changes from baseline.

Comparison groups	Results at post-treatment visits v Results at baseline
-------------------	--

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[9]
P-value	> 0.05 ^[10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[10] - There was no statistically significant change in heart rate during the study.

Primary: Electrocardiogram recordings

End point title	Electrocardiogram recordings
End point description:	
Single 12-lead electrocardiogram (ECG) was recorded after 10 minutes of supine rest using an ECG machine. PQ/PR, QRS, QT and QTcH intervals were recorded. All ECG data were listed for each patient and summarised as vital signs parameters. The baseline was defined as the last measurement prior to first dose of the test product (i.e. measurement at Visit 1a).	
End point type	Primary
End point timeframe:	
Visit 1a (screening) and Visit 7(day 36, follow-up)	

End point values	Safety analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[11]	
Units: msec				
arithmetic mean (standard deviation)				
QTcF Interval, Aggregate at Visit 1a	409.2 (± 21.2)	409.2 (± 21.2)	409.2 (± 21.2)	
QTcF Interval, Aggregate at Visit 7	411.4 (± 19.0)	411.4 (± 19.0)	411.4 (± 19.0)	
QT Interval, Aggregate at Visit 1a	400.0 (± 30.6)	400.0 (± 30.6)	400.0 (± 30.6)	
QT Interval, Aggregate at Visit 7	394.8 (± 28.5)	394.8 (± 28.5)	394.8 (± 28.5)	
PR Interval, Aggregate at Visit 1a	168.5 (± 20.6)	168.5 (± 20.6)	168.5 (± 20.6)	
PR Interval, Aggregate at Visit 7	170.0 (± 20.6)	170.0 (± 20.6)	170.0 (± 20.6)	
QRS Duration, Aggregate at Visit 1a	98.3 (± 20.7)	98.3 (± 20.7)	98.3 (± 20.7)	
QRS Duration, Aggregate at Visit 7	98.8 (± 18.8)	98.8 (± 18.8)	98.8 (± 18.8)	

Notes:

[11] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Statistical analyses

Statistical analysis title	No change in ECG parameters
Statistical analysis description:	
The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the safety analysis set to assess the statistical significance of changes from baseline.	
Comparison groups	Results at baseline v Results at post-treatment visits

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[12]
P-value	> 0.05 ^[13]
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[13] - There was no statistically significant change in any of the ECG parameters from baseline to Visit 7 (first follow-up)

Primary: Vital signs-body temperature

End point title	Vital signs-body temperature
-----------------	------------------------------

End point description:

Body temperature was measured in supine position after 5 minutes of rest using the same method each time. The baseline was defined as the last measurement prior to first dose of the test product (i.e. measurement at Visit 2). Data were presented by visit for each parameter and patient and summarised using summary statistics, including absolute and percent change from baseline (Visit 2).

End point type	Primary
----------------	---------

End point timeframe:

Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)

End point values	Safety analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[14]	
Units: celsius				
arithmetic mean (standard deviation)				
Body temperature at baseline (Visit 2)	36.61 (± 0.23)	36.61 (± 0.23)	36.61 (± 0.23)	
Body temperature at Visit 6	36.48 (± 0.20)	36.48 (± 0.20)	36.48 (± 0.20)	

Notes:

[14] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Statistical analyses

Statistical analysis title	No change in body temperature
----------------------------	-------------------------------

Statistical analysis description:

The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the safety analysis set to assess the statistical significance of changes from baseline.

Comparison groups	Results at baseline v Results at post-treatment visits
-------------------	--

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[15]
P-value	> 0.05 ^[16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[16] - There was no statistically significant change in body temperature during the study

Primary: Clinical chemistry parameters

End point title	Clinical chemistry parameters
-----------------	-------------------------------

End point description:

Clinical chemistry parameters assessed:

Sodium
Potassium
Chloride
Calcium
Albumin
Aspartate aminotransferase (AST)
Alkaline Phosphatase
Alanine aminotransferase (ALT)
Creatinine
Creatinine kinase
Myoglobin
C-reactive protein (CRP)
Total bilirubin
Glucose (non-fasting)

Data were presented by visit for each parameter and patient and summarised using summary statistics, including absolute and percent change from baseline (Visit 2). The overall significance level was 5%.

End point type	Primary
----------------	---------

End point timeframe:

Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)

End point values	Safety analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[17]	
Units: percentage				
arithmetic mean (standard deviation)				
Relative increase in bilirubin at Visit 5	18.7 (± 31.7)	18.7 (± 31.7)	18.7 (± 31.7)	
Relative increase in glucose at Visit 8	11.5 (± 14.9)	11.5 (± 14.9)	11.5 (± 14.9)	
Relative decrease in creatinine at Visit 6	5.3 (± 6.3)	5.3 (± 6.3)	5.3 (± 6.3)	
Relative decrease in myoglobin at Visit 7	15.0 (± 20.1)	15.0 (± 20.1)	15.0 (± 20.1)	

Notes:

[17] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Statistical analyses

Statistical analysis title	Changes in clinical chemistry parameters
-----------------------------------	--

Statistical analysis description:

The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the safety analysis set to assess the statistical significance of changes from baseline.

Comparison groups	Results at baseline v Results at post-treatment visits
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[18]
P-value	< 0.05 ^[19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[19] - Statistically significant mean changes from baseline: bilirubin (Visit 5), creatinine (Visit 6), myoglobin (Visit 7) and glucose (Visit 8).

Primary: Haematology

End point title	Haematology
-----------------	-------------

End point description:

Haematological parameters assessed:

Haemoglobin (Hb)

Haemoglobin S (only at screening)

Haemoglobin A1c (only at screening)

Red blood cells (RBC)

White blood cells (WBC)

Differential cell count

Platelets (thrombocytes)

Data were presented by visit for each parameter and patient and summarised using summary statistics, including absolute and percent change from baseline (Visit 2). The overall significance level was 5%.

End point type	Primary
----------------	---------

End point timeframe:

Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)

End point values	Safety analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[20]	
Units: percentage				
arithmetic mean (standard deviation)				
Relative decrease in Hb at Visit 6	3.7 (± 4.1)	3.7 (± 4.1)	3.7 (± 4.1)	
Relative decrease in Hb at Visit 7	3.6 (± 4.4)	3.6 (± 4.4)	3.6 (± 4.4)	
Relative decrease in erythrocytes at Visit 6	2.8 (± 2.9)	2.8 (± 2.9)	2.8 (± 2.9)	
Relative decrease in erythrocytes at Visit 7	2.8 (± 4.1)	2.8 (± 4.1)	2.8 (± 4.1)	
Relative increase in leukocytes at Visit 8	16.7 (± 25.8)	16.7 (± 25.8)	16.7 (± 25.8)	
Relative increase in lymphocytes at Visit 5	10.5 (± 14.6)	10.5 (± 14.6)	10.5 (± 14.6)	

Relative increase in lymphocytes at Visit 7	8.3 (± 11.6)	8.3 (± 11.6)	8.3 (± 11.6)	
Relative increase in erythrocytes at Visit 9	3.9 (± 4.4)	3.9 (± 4.4)	3.9 (± 4.4)	
Relative increase in neutrophils at Visit 8	25.8 (± 37.5)	25.8 (± 37.5)	25.8 (± 37.5)	
Relative increase in platelets at Visit 5	5.7 (± 6.5)	5.7 (± 6.5)	5.7 (± 6.5)	

Notes:

[20] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Statistical analyses

Statistical analysis title	Changes in haematological parameters
-----------------------------------	--------------------------------------

Statistical analysis description:

The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the safety analysis set to assess the statistical significance of changes from baseline.

Comparison groups	Results at baseline v Results at post-treatment visits
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[21]
P-value	< 0.05 ^[22]
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[22] - There were statistically significant relative changes in Hb (Visits 6 and 7), erythrocytes (Visits 6, 7 and 9), leukocytes (Visit 8), platelets (Visit 5), lymphocytes (Visits 5 and 7) and neutrophils (Visit 8).

Primary: Haemostatic parameters

End point title	Haemostatic parameters
-----------------	------------------------

End point description:

Haemostatic parameters assessed:

Effect activated partial thromboplastin time (APTT): Visit 1a, Visit 2 and Visit 6 (15 min pre-dose, 30 min post-dose, 1 hour post-dose, 2 hours post-dose, 2.5 hours post-dose, 3 hours post-dose, 4 hours post-dose and 6 hours post-dose)

Fibrinogen: Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)

Von Willebrand factor (vW antigen, vW activity + factor VIII): Visit 1a (screening)

Prothrombin intl. normalized ratio (PK-INR): Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)

Data were presented by patient and assessment time as changes from baseline, using summary statistics. The overall significance level was 5%. Statistics were presented for all factors except APTT.

End point type	Primary
----------------	---------

End point timeframe:

APTT: Visit 1a (screening), Visit 2 (day 1 of treatment) and Visit 6 (day 29 of treatment)

Fibrinogen and PK-INR: total study

Von Willebrand factor :Visit 1a (screening)

End point values	Safety analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[23]	
Units: second				
arithmetic mean (standard deviation)				
APTT at baseline (Visit 2, 15 min pre-dose)	26.5 (± 1.5)	26.5 (± 1.5)	26.5 (± 1.5)	
APTT at the end of the study (Visit 9)	26.8 (± 2.0)	26.8 (± 2.0)	26.8 (± 2.0)	
APTT at Visit 2, 6 hours post-dose	29.2 (± 2.0)	29.2 (± 2.0)	29.2 (± 2.0)	

Notes:

[23] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Attachments (see zip file)	APTT.docx
-----------------------------------	-----------

Statistical analyses

Statistical analysis title	Changes in haemostatic parameters
-----------------------------------	-----------------------------------

Statistical analysis description:

The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the safety analysis set to assess the statistical significance of changes from baseline.

Comparison groups	Results at baseline v Results at post-treatment visits
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[24]
P-value	> 0.05 ^[25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[25] - There was no statistically significant change in any of the haemostatic parameters assessed during the study.

Secondary: Functional rating with ALS Functional Rating Scale – Revised (ALSFRS-R)

End point title	Functional rating with ALS Functional Rating Scale – Revised (ALSFRS-R)
-----------------	---

End point description:

Disease severity was evaluated by the Investigator using the ALSFRS-R rating scale in an interview with the patient at Visit 1a (Screening), pre-dose at Visits 2-5 (treatment) and Visits 7-9 (follow-up). ALSFRS measured 12 different functions (speech, salivation, swallowing, handwriting, cut food and use utensils, dressing and hygiene, turning in bed and adjusting the bedding, walking, climbing stairs, dyspnea, orthopnea and respiratory insufficiency). For each function, 0 to 4 points were assigned, where 0= worst and 4= best. The total ALSFRS score was the sum of all points collected. The baseline was defined as the last measurement prior to first dose of the test product (i.e. measurement at Visit 2). The parameters were presented as changes from baseline using summary statistics. The overall significance level was 5%. The statistical test used was non-parametric Wilcoxon signed rank sum test, for within patient changes over time.

End point type	Secondary
----------------	-----------

End point timeframe:

Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)

End point values	Full analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[26]	
Units: points				
arithmetic mean (standard deviation)				
Total score at baseline	36.2 (± 6.7)	36.2 (± 6.7)	36.2 (± 6.7)	
Total score at Visit 6	39.2 (± 6.3)	39.2 (± 6.3)	39.2 (± 6.3)	
Relative increase (%) from baseline to Visit 6	9.2 (± 7.5)	9.2 (± 7.5)	9.2 (± 7.5)	
Relative increase (%) from baseline to Visit 7	7.6 (± 6.6)	7.6 (± 6.6)	7.6 (± 6.6)	
Relative increase (%) from baseline to Visit 8	7.9 (± 8.4)	7.9 (± 8.4)	7.9 (± 8.4)	

Notes:

[26] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Statistical analyses

Statistical analysis title	Increase in total mean ALSFRS-R score
Statistical analysis description:	
The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the full analysis set to assess the statistical significance of changes from baseline.	
Comparison groups	Results at baseline v Results at post-treatment visits
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[27]
P-value	< 0.05 ^[28]
Method	Wilcoxon (Mann-Whitney)

Notes:

[27] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[28] - There was a statistically significant increase of total mean ALSFRS-R score during the treatment phase and at the follow-up Visits 7 and 8 (p< 0.05)

Secondary: Functional rating with Norris scale

End point title	Functional rating with Norris scale
End point description:	
Disease severity was evaluated by the Investigator using the Norris rating scale in an interview with the patient at Visit 1a (Screening), pre-dose at Visits 2-5 (treatment) and Visits 7-9 (follow-up). Norris measured 34 different functions. For each function, 0 to 3 points were assigned, where 0= missing, 1= weak, 2= reduced and 3= normal. The total Norris score was the sum of all points collected. The baseline was defined as the last measurement prior to first dose of the test product (i.e. measurement at Visit 2). The parameters were presented as changes from baseline using summary statistics. The overall significance level was 5%. The statistical test used was non-parametric Wilcoxon signed rank sum test, for within patient changes over time.	
End point type	Secondary

End point timeframe:

Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)

End point values	Full analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[29]	
Units: points				
arithmetic mean (standard deviation)				
Total score at baseline	70.8 (± 14.1)	70.8 (± 14.1)	70.8 (± 14.1)	
Total score at Visit 6	78.3 (± 12.6)	78.3 (± 12.6)	78.3 (± 12.6)	
Relative increase (%) from baseline to Visit 6	12.1 (± 12.9)	12.1 (± 12.9)	12.1 (± 12.9)	
Relative increase (%) from baseline to Visit 7	11.0 (± 13.7)	11.0 (± 13.7)	11.0 (± 13.7)	
Relative increase (%) from baseline to Visit 8	10.8 (± 11.1)	10.8 (± 11.1)	10.8 (± 11.1)	

Notes:

[29] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Statistical analyses

Statistical analysis title	Increase in total mean Norris score
----------------------------	-------------------------------------

Statistical analysis description:

The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the full analysis set to assess the statistical significance of changes from baseline.

Comparison groups	Results at baseline v Results at post-treatment visits
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[30]
P-value	< 0.05 ^[31]
Method	Wilcoxon (Mann-Whitney)

Notes:

[30] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[31] - There was a gradual increase of total mean score during the treatment phase, which was statistically significant at Visits 4, 5 and 6 and during follow-up at Visits 7 and 8 (p< 0.05) .

Secondary: Biomarkers for neurological diseases

End point title	Biomarkers for neurological diseases
-----------------	--------------------------------------

End point description:

Extent of presence of biomarkers for neurological diseases was evaluated in serum, plasma and CSF sampled at Visit 1b and Visit 7.

Biomarkers assessed:

In CSF: Albumin, Immunoglobulin G and M (IgG and IgM), IgG index, IgM index, Tau, Phosphorylated Tau, NFL, Beta-amyloid, glial fibrillary acidic protein (GFAP) and Compleasome

In serum: Albumin, IgG and IgM

In plasma: NFL and Compleasome

All biomarkers were presented, using summary statistics, as changes from baseline (Visit 1b) to Visit 7. The overall significance level was 5%. The statistical test used was non-parametric Wilcoxon signed rank sum test, for within patient changes over time.

End point type	Secondary
End point timeframe:	
Visit 1b (screening) and Visit 7 (Day 36, follow-up)	

End point values	Safety analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[32]	
Units: mg/L				
arithmetic mean (standard deviation)				
Serum IgM at baseline	884 (± 447)	884 (± 447)	884 (± 447)	
Serum IgM at Visit 7	849 (± 493)	849 (± 493)	849 (± 493)	
CSF IgM index at baseline	0.047 (± 0.016)	0.047 (± 0.016)	0.047 (± 0.016)	
CSF IgM index at Visit 7	0.050 (± 0.016)	0.050 (± 0.016)	0.050 (± 0.016)	

Notes:

[32] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Attachments (see zip file)	Biomarkers.pdf
-----------------------------------	----------------

Statistical analyses

Statistical analysis title	Changes in biomarkers
-----------------------------------	-----------------------

Statistical analysis description:

The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the full analysis set to assess the statistical significance of changes from baseline.

Comparison groups	Results at baseline v Results at post-treatment visits
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[33]
P-value	< 0.05 ^[34]
Method	Wilcoxon (Mann-Whitney)

Notes:

[33] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[34] - There was a decrease in serum IgM (p= 0.006) and an increase in CSF IgM index (p=0.023) from baseline to Follow-up Visit 7. No other statistically significant changes were found in any of the other biomarkers.

Secondary: Pulmonary function

End point title	Pulmonary function
-----------------	--------------------

End point description:

Pulmonary function was measured as percentage of Forced Vital Capacity (FVC) at Visit 1a (Screening), pre-dose at Visits 2-5 (treatment) and Visits 7-9 (follow-up). The baseline was defined as the last measurement prior to first dose of the test product (i.e. measurement at Visit 2). The overall significance level was 5%. The statistical test used was non-parametric Wilcoxon signed rank sum test, for within patient changes over time.

The mean FVC at baseline (Visit 2) was 84.60% (SD 13.74). Statistically significant changes from this baseline are presented below.

End point type	Secondary
End point timeframe:	
Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)	

End point values	Safety analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[35]	
Units: percentage				
arithmetic mean (standard deviation)				
Relative decrease in FVC from baseline to Visit 6	4.6 (± 3.1)	4.6 (± 3.1)	4.6 (± 3.1)	
Relative decrease in FVC from baseline to Visit 8	7.2 (± 7.7)	7.2 (± 7.7)	7.2 (± 7.7)	
Relative decrease in FVC from baseline to Visit 9	9.0 (± 7.0)	9.0 (± 7.0)	9.0 (± 7.0)	

Notes:

[35] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Attachments (see zip file)	FVC.docx
-----------------------------------	----------

Statistical analyses

Statistical analysis title	Decrease in FVC
-----------------------------------	-----------------

Statistical analysis description:

The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the full analysis set to assess the statistical significance of changes from baseline.

Comparison groups	Results at baseline v Results at post-treatment visits
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[36]
P-value	< 0.05 ^[37]
Method	Wilcoxon (Mann-Whitney)

Notes:

[36] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[37] - There was a statistically significant decrease in mean FVC at the last dosing day (Visit 6), and at the follow-up Visit 8 and Visit 9.

Secondary: Quality of life

End point title	Quality of life
-----------------	-----------------

End point description:

The patient's quality of life (QoL) was evaluated using a visual analogue scale (VAS)-based questionnaire on a scale of 0 to 100, where 0= very bad and 100= very good) which was filled out by the patient and, if applicable, a next of kin. The same next of kin was used throughout the study. The baseline was defined as the last measurement prior to first dose of the test product (i.e. measurement at Visit 2). QoL was reported as changes from baseline using summary statistics.

End point type	Secondary
----------------	-----------

End point timeframe:

Total study: Visit 1a (Screening), pre-dose at Visits 2, 4 and 6 (days 1, 15 and 29, treatment period) and Visit 8 (days 50, follow-up)

End point values	Full analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[38]	
Units: points				
arithmetic mean (standard deviation)				
Max mean QoL score at baseline (Visit 2)	56.2 (± 13.7)	56.2 (± 13.7)	56.2 (± 13.7)	
Min mean QoL score at baseline (Visit 2)	43.6 (± 17.1)	43.6 (± 17.1)	43.6 (± 17.1)	
Max mean QoL score at Visit 6	63.5 (± 20.6)	63.5 (± 20.6)	63.5 (± 20.6)	
Min mean QoL score at Visit 6	39.2 (± 19.6)	39.2 (± 19.6)	39.2 (± 19.6)	

Notes:

[38] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Statistical analyses

Statistical analysis title	No changes in QoL
----------------------------	-------------------

Statistical analysis description:

The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the full analysis set to assess the statistical significance of changes from baseline.

Comparison groups	Results at baseline v Results at post-treatment visits
-------------------	--

Number of subjects included in analysis	26
---	----

Analysis specification	Pre-specified
------------------------	---------------

Analysis type	other ^[39]
---------------	-----------------------

P-value	> 0.05 ^[40]
---------	------------------------

Method	Wilcoxon (Mann-Whitney)
--------	-------------------------

Notes:

[39] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[40] - No changes in mean QoL score from baseline to the rest of the study.

Secondary: Autonomous symptoms

End point title	Autonomous symptoms
-----------------	---------------------

End point description:

Prevalence and extent of 16 sensory and autonomous symptoms were recorded by the Investigator in an interview with the patient. The measuring scale was the following: 0= no symptoms, 1= some symptoms, 2= moderate number of symptoms and 3= many symptoms. These parameters were presented as changes from baseline using summary statistics. The overall significance level was 5%. The statistical test used was non-parametric Wilcoxon signed rank sum test, for within patient changes over time.

The total score mean value was 6.2 (SD= 3.5) at baseline (Visit 2) and it was significantly decreased throughout the study ($p < 0.05$). Changes from baseline to Visit 6 (last treatment day) and to Visit 9 (last follow-up) are presented below.

End point type	Secondary
----------------	-----------

End point timeframe:

Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (days 1, 8, 15, 22 and 29, treatment) and Visits 7-9 (days 36, 50 and 99, follow-up)

End point values	Safety analysis set	Results at baseline	Results at post-treatment visits	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13 ^[41]	
Units: percentage				
arithmetic mean (standard deviation)				
Relative decrease in total score at Visit 6	39.0 (± 48.3)	39.0 (± 48.3)	39.0 (± 48.3)	
Relative decrease in total score at Visit 9	43.3 (± 41.1)	43.3 (± 41.1)	43.3 (± 41.1)	

Notes:

[41] - This is not a separate analysis set but reports data for the same 13 subjects as at baseline.

Statistical analyses

Statistical analysis title	Decrease in total score
-----------------------------------	-------------------------

Statistical analysis description:

The subgroups "Results at baseline" and "Results at post-treatment visits" were only defined in this report in order to describe the statistical analysis. No such analysis sets were used in the study. The statistical analysis was performed within the full analysis set to assess the statistical significance of changes from baseline.

Comparison groups	Results at baseline v Results at post-treatment visits
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other ^[42]
P-value	< 0.05 ^[43]
Method	Wilcoxon (Mann-Whitney)

Notes:

[42] - non-parametric Wilcoxon signed rank sum test.

This was a within-group comparison in this single-arm study. The number of subjects analyzed shown above as N=26 is incorrect and is due to an innate error of the EudraCT system. The correct number of subjects analyzed for this evaluation is N=13.

[43] - The mean score was reduced (relative change) to nearly half at the last dosing day (Visit 6, $p = 0.024$) and at the end of the study (Visit 9, $p = 0.008$).

Secondary: Hepatocyte Growth factor

End point title	Hepatocyte Growth factor
-----------------	--------------------------

End point description:

Blood samples for Hepatocyte Growth Factor (HGF) measurement were collected through venepuncture or through an indwelling venous catheter into a vacutainer tube with citrate. The HGF levels were presented by patient and assessment time as changes from baseline, using summary statistics. The baseline was defined as the last measurement prior to first dose of the test product (i.e. measurement at Visit 2 ,15 min pre-dose).

End point type	Secondary
----------------	-----------

End point timeframe:

Visit 2 (Day 1, treatment) and Visit 6 (day 29, treatment): 15 min pre-dose, 30 min post-dose, 1 hour post-dose, 2 hours post-dose, 2.5 hours post-dose, 3 hours post-dose, 4 hours post-dose and 6 hours post-dose

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: pg/mL				
arithmetic mean (standard deviation)				
HGF at Visit 6, 15 min pre-dose	724.6 (± 223.6)			
HGF at Visit 2, 15 min pre-dose	820.0 (± 580.9)			
HGF at Visit 2, 2 hours post-dose	37863.1 (± 14235.1)			
HGF at Visit 6, 2.5 hours post-dose	41613.1 (± 9768.1)			

Attachments (see zip file)	HGF.docx
-----------------------------------	----------

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ILB- time to maximum concentration

End point title	Pharmacokinetics of ILB- time to maximum concentration
-----------------	--

End point description:

Descriptive statistics for time to maximum concentration (tmax) were presented after first and last ILB administration (Visit 2 and Visit 6), as well as pooled data over the dosing days (if appropriate).

End point type	Secondary
----------------	-----------

End point timeframe:

Visit 2 (treatment day 1) to Visit 6 (treatment day 29)

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: hours				
median (full range (min-max))				
tmax on Day 1 (Visit 2)	2.48 (1.95 to 3.02)			
tmax on Day 29 (Visit 6)	2.00 (0.98 to 2.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ILB- maximum concentration

End point title	Pharmacokinetics of ILB- maximum concentration
End point description: Descriptive statistics for maximum concentration (C _{max}) were presented after first and last ILB administration (Visit 2 and Visit 6), as well as pooled data over the dosing days (if appropriate).	
End point type	Secondary
End point timeframe: Visit 2 (treatment day 1) to Visit 6 (treatment day 29)	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: mg/L				
median (full range (min-max))				
C _{max} on Day 1 (Visit 2)	3.30 (2.15 to 4.40)			
C _{max} on Day 29 (Visit 6)	3.86 (2.94 to 4.51)			

Attachments (see zip file)	PK graph.docx
-----------------------------------	---------------

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of ILB-terminal elimination

End point title	Pharmacokinetics of ILB-terminal elimination
End point description: Descriptive statistics for the terminal elimination (t _{1/2}) were presented after first and last ILB administration (Visit 2 and Visit 6), as well as pooled data over the dosing days (if appropriate).	

End point type	Secondary
End point timeframe:	
Visit 2 (treatment day 1) to Visit 6 (treatment day 29)	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: hours				
median (full range (min-max))				
t½ on Day 1(Visit 2)	2.86 (1.55 to 4.80)			
t½ on Day 29 (Visit 6)	2.22 (1.36 to 3.23)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Total study: Visit 1a (Screening), pre-dose at Visits 2-5 (treatment) and Visits 7-9 (follow-up)

Adverse event reporting additional description:

All adverse events (AEs) and SAEs were recorded from start of IMP administration until the end of follow-up (Visit 9). Adverse events that occurred before first IMP treatment were reported separately as baseline events. All AEs presented are treatment-emergent AEs (TEAEs).

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	20.1
--------------------	------

Reporting groups

Reporting group title	Overall trial
-----------------------	---------------

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 13 (84.62%)		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		
Head injury			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin injury</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Subcutaneous haematoma</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 13 (7.69%)</p> <p>1</p> <p>1 / 13 (7.69%)</p> <p>1</p> <p>1 / 13 (7.69%)</p> <p>1</p>		
<p>Nervous system disorders</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 13 (7.69%)</p> <p>1</p>		
<p>General disorders and administration site conditions</p> <p>Fatigue</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Puncture site haemorrhage</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 13 (7.69%)</p> <p>2</p> <p>1 / 13 (7.69%)</p> <p>1</p> <p>1 / 13 (7.69%)</p> <p>2</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Acne</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 13 (7.69%)</p> <p>1</p>		
<p>Psychiatric disorders</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 13 (7.69%)</p> <p>1</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p>	<p>1 / 13 (7.69%)</p> <p>1</p>		

subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2018	<p>CSP Section 9.1 Added that a patient can be re-screened, because it was not clearly described in the previous CSP version.</p> <p>CSP Sections 9.3 and 9.4 Replaced inclusion criterion #6 with exclusion criterion #12, to clarify that only patients with clinically significant abnormal PK-INR, fibrinogen, von Willebrand factor and APTT at screening should be excluded. This change was made because this information was more clearly expressed as an inclusion criterion.</p> <p>CSP Section 16.7.4 Addition of interim analysis, as an extra review of effects and security.</p>
11 July 2019	<p>CSP Section 12.3.7 Addition of pregnancy reporting, because it was not included in the previous CSP version, but it is mandatory according to the IHC-GCP.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 August 2019	The planned number of patients to be included in the study was 15, however due to delays in recruitment, and the fact that no SAEs or other safety concerns were reported, it was decided by the Sponsor to terminate patient recruitment and conclude the study with 13 patients.	-

Notes:

Limitations and caveats

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

There were 44 protocol deviations reported and they were mainly related to GCP compliance, missing laboratory data and violations of inclusion/exclusion criteria. Other protocol deviations were related to schedule/timing of assessments.

Notes: