Clinical trial results:
Evaluation of the safety, tolerability, efficacy and immunological responses of the interleukin-2 analogue Aldesleukin (Proleukin®) in the treatment of systemic lupus erythematosus as prototypic autoimmune disease (PRO-IMMUN).

A COMBINED PHASE I/IIA, PROSPECTIVE, OPEN-LABEL AND UNCONTROLLED SINGLE-CENTER STUDY TO ANALYSE SAFETY, TOLERABILITY, EFFICACY AND IMMUNOLOGICAL RESPONSES OF LOW-DOSE SUBCUTANEOUS INTERLEUKIN-2 (ALDESLEUKIN, PROLEUKIN®) IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND INCREASED DISEASE ACTIVITY REFRACTORY TO STANDARD THERAPIES.

Summary

EudraCT number	2013-001599-40
Trial protocol	DE
Global end of trial date	19 October 2018

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022
Summary attachment (see zip file)	Final Study Report (PRO-IMMUN_Clinical Study Report_Final.pdf)

Trial information

Trial identification

Sponsor protocol code	23032013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00004858

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Organisationseinheit für Neue Therapien (Studienabteilung), Charité - Universitätsmedizin Berlin Rheumatologie und klinische Immunologie, CC12, +49 30450 513 061, gerd.burmester@charite.de
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	513 061, gerd.burmester@charite.de

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	26 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2018
Global end of trial reached?	Yes
Global end of trial date	19 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of PRO-IMMUN was to evaluate the safety, tolerability and the effects on the Treg population of a cyclic subcutaneous low-dose interleukin-2 regimen using the recombinant human interleukin-2 analogue aldesleukin (Proleukin®) in SLE patients with moderate-to-severe disease activity despite previous treatment with at least two conventional therapies.
The primary endpoint was the number of patients who achieved at least a 100% increase (2-fold) in the proportion of CD25hi-expressing cells among circulating CD3+CD4+FoxP3+CD127lo Treg at day 62 (week 9; one day after the 4th treatment cycle) compared to baseline at day 1 (before the 1st treatment cycle).
Safety and tolerability were evaluated descriptively by assessment of the incidence, frequency, duration, severity, toxicity grade and the causal relationship to the study medication of any adverse event at every scheduled visit after the screening visit (Visits 2-11) and at every unscheduled visit.

Protection of trial subjects:

To ensure trial subjects safety study visits took place every 5 to 16 days during the treatment phase (9 weeks) including a detailed physical examination with vital signs (axillary body temperature, pulse rate in resting position, systolic and diastolic blood pressure in resting position), asssesements of disease activity, tolerability, AEs and comprehensive safety laboratory and immunological analyses. Follow-up visits took place 3 weeks (week 12) and 9 weeks (week 18) after last dosing of the IMP.
To minimize IMP-associated AEs such as fever, chills, myalgia or arthralgia, patients were recommended to take 500-1000mg of paracetamol prior to s.c. application of the IMP.
Diagnostic safety procedures including a 12-lead electrocardiogram, an echocardiography, an abdominal ultrasound and lung function tests were performed during the screening and the follow-up period.
At screening and before each of the four treatment cycles the Eastern Cooperative Oncology Group (ECOG) performance status was determined. Patients with an ECOG grade of two or more were not eligible to participate or to continue to participate in this study.

Background therapy:

Corticosteroids at daily doses of ≤ 30mg prednisolone (or equivalent) orally and the following standard-of-care immunosuppressive therapies at stable doses for least 4 weeks prior to the first administration

of the IMP (day 1) at the indicated dose ranges:
- Azathioprine: 1-2 mg/kg/day orally
- Chloroquine or hydroxychloroquine: 200-400 mg/d orally
- Mycophenolate mofetil (MMF): 1-3g/d orally
- NSAID: oral doses as indicated and allowed

Changes in the daily dose of corticosteroids during the study were allowed if considered appropriate by investigator.

Evidence for comparator:	
Single-arm study without active comparator	
Actual start date of recruitment	31 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between March 31, 2014, and May 27, 2016 from the in– and outpatient clinic of the Medizinische Klinik mit Schwerpunkt Rheumatologie und Klinische Immunologie of the Charité – Universitätsmedizin Berlin, Germany

Pre-assignment

Screening details:

Between March 31, 2014, and May 27, 2016, 13 patients were screened for pre-specified inclusion and exclusion critieria, of whom 10 met the eligibility criteria and were enrolled in the trial.

Period 1

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

Arms

Arm title	Low-dose IL-2

Arm description:

The therapeutic regimen consisted of four separate treatment cycles each with daily subcutaneous injections of different doses of aldesleukin for five consecutive days. A consecutive increase of the administered single daily dose of aldesleukin from the previous cycle to the subsequent cycle was scheduled in order to assess the tolerability and the dose-dependency of observed effects.
Dose adaptations during the treatment period were applied according to defined dose adaption criteria.
Used single doses of aldesleukin: 0.75 million IU, 1.5 million IU and 3.0 million IU per day

Arm type	Experimental
Investigational medicinal product name	Aldesleukin
Investigational medicinal product code	L03A C01
Other name	Proleukin
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The therapeutic regimen consisted of four treatment cycles each with daily subcutaneous injections of aldesleukin for five consecutive days separated by washout periods of 9 to 16 days in between the cycles.
Dose adaptions of the administered daily dose of aldesleukin in the subsequent cycles were conducted according to defined dose adaption criteria. The decision to reduce, maintain or increase the single daily dose in the subsequent treatment cycle was based on clinical, laboratory and immunological findings obtained during the previous cycle.

Administered daily dosages per cycle:
1st cycle: 1.5 million IU (7.5 million IU in total)
2nd cycle: 0.75 or 3.0 million IU (3.75 or 15 million IU in total)
3rd cycle: 0.75 or 1.5 million IU (7.5 or 15 million IU in total)
4th cycle: 0.75 or 1.5 million IU (7.5 or 15 million IU in total)

Number of subjects in period 1	Low-dose IL-2
Started	10
Completed	9
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Mean age (range): 37.7 years (26-54 years) Sex: 1 male, 9 females Mean disease duration (range): 13.3 years (2-35 years) Mean SELENA-SLEDAI score (range): 10 (6-16) Mean daily dose of corticosteroids (range): 9.25 mg/day (5-20 mg/day)	

Reporting group values	Overall trial	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
Adults (18-64 years)	10	10	
Age continuous			
Mean age (range): 37.7 years (26-54 years)			
Units: years arithmetic mean full range (min-max)	 37.7 26 to 54	 -	
Gender categorical Units: Subjects			
Female Male	9 1	9 1	
Disease duration			
Mean disease duration (range): 13.3 years (2-35 years)			
Units: years arithmetic mean full range (min-max)	 13.3 2 to 35	 -	
SELENA-SLEDAI score			
Disease activity measure Mean SELENA-SLEDAI score (range): 10 (6-16)			
Units: points arithmetic mean full range (min-max)	 10 6 to 16	 -	
Corticosteroid dose			
Mean daily dose of corticosteroids (range): 9.25 mg/day (5-20 mg/day)			
Units: mg/day arithmetic mean full range (min-max)	 9.25 5 to 20	 -	

End points

End points reporting groups

Reporting group title	Low-dose IL-2

Reporting group description:

The therapeutic regimen consisted of four separate treatment cycles each with daily subcutaneous injections of different doses of aldesleukin for five consecutive days. A consecutive increase of the administered single daily dose of aldesleukin from the previous cycle to the subsequent cycle was scheduled in order to assess the tolerability and the dose-dependency of observed effects.
Dose adaptations during the treatment period were applied according to defined dose adaption criteria.
Used single doses of aldesleukin: 0.75 million IU, 1.5 million IU and 3.0 million IU per day

Subject analysis set title	Analysis population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Definition of analysed population: The primary efficacy endpoint and all secondary endpoints were assessed in all patients who completed at least one treatment cycle (intention-to-treat population excluding screening failures). Last-observation-carried-forward (LOCF) modality was applied for non-completer.

Primary: Treg response

End point title	Treg response

End point description:

Number of patients who achieved at least a 100% increase from baseline in the proportion of CD25hi-expressing cells among circulating CD3+CD4+FoxP3+CD127lo regulatory T cells at day 62 (after four treatment cycles)

End point type	Primary

End point timeframe:

day 1 to day 62

End point values	Low-dose IL-2	Analysis population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: number				
100% increase from baseline	0	9		

Statistical analyses

Statistical analysis title	Treg response (continuous variables)

Statistical analysis description:

Change from baseline in the proportion of CD25hi-expressing cells among circulating CD3+CD4+FOXP3+CD127lo regulatory T cells at day 62

Comparison groups	Low-dose IL-2 v Analysis population

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	22.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.75
upper limit	32.53
Variability estimate	Standard deviation
Dispersion value	11.03

Notes:

[1] - Two-sided Wilcoxon signed-rank test was used to compare changes in the proportion of CD25hi-expressing cells among circulating CD3+CD4+FOXP3+CD127lo regulatory T cells between baseline and day 62

Secondary: Clinical response: SELENA-SLEDAI

End point title	Clinical response: SELENA-SLEDAI

End point description:

Absolute change from baseline in SELENA-SLEDAI score at day 62

End point type	Secondary

End point timeframe:

Day 1 to day 62

End point values	Low-dose IL-2	Analysis population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: points				
median (inter-quartile range (Q1-Q3))	10.0 (7.5 to 12.5)	5.0 (4.0 to 12.25)		

Statistical analyses

Statistical analysis title	Clinical response (continuous variables)

Statistical analysis description:

Absolute change from baseline in SLENA-SLEDAI score at day 62

Comparison groups	Low-dose IL-2 v Analysis population

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.041
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.295
upper limit	-0.5048
Variability estimate	Standard deviation
Dispersion value	3.348

Secondary: Clinical response: PGA

End point title	Clinical response: PGA
End point description: Absolute change from baseline in PGA score at day 62	
End point type	Secondary
End point timeframe: day 1 to day 62	

End point values	Low-dose IL-2	Analysis population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: points				
median (inter-quartile range (Q1-Q3))	1.75 (1.5 to 2.125)	1.25 (0.5 to 2.0)		

Statistical analyses

Statistical analysis title	Clinical response PGA (continuous variables)
Comparison groups	Low-dose IL-2 v Analysis population
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0039
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	-0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9677
upper limit	-0.3823
Variability estimate	Standard deviation
Dispersion value	0.4091

Secondary: Serological response: C3

End point title	Serological response: C3
End point description:	
Change from baseline in serum concentrations of the complement factor C3 at day 62	
End point type	Secondary
End point timeframe:	
day 1 to day 62	

End point values	Low-dose IL-2	Analysis population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: mg/L				
median (inter-quartile range (Q1-Q3))	775 (605 to 795)	805 (737.5 to 832.5)		

Statistical analyses

Statistical analysis title	Serological response C3 (continuous variables)
Comparison groups	Low-dose IL-2 v Analysis population
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0078
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	30
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.17
upper limit	117.8
Variability estimate	Standard deviation
Dispersion value	72.45

Secondary: Serological response: C4	
End point title	Serological response: C4
End point description: Change from baseline in concentration of the complement factor C4 at day 62	
End point type	Secondary
End point timeframe: day 1 to day 62	

End point values	Low-dose IL-2	Analysis population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: mg/L				
median (inter-quartile range (Q1-Q3))	95 (75 to 122.5)	100 (67.5 to 135)		

Statistical analyses

Statistical analysis title	Serological response C4 (continuous variables)
Comparison groups	Low-dose IL-2 v Analysis population
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1875
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.954
upper limit	15.95
Variability estimate	Standard deviation
Dispersion value	12.52

Secondary: Serological response: anti-dsDNA-Abs	
End point title	Serological response: anti-dsDNA-Abs
End point description: Change from baseline in concentration of anti-dsDNA-antibodies at day 62	
End point type	Secondary

End point timeframe: day 1 to day 62

End point values	Low-dose IL-2	Analysis population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: U/mL				
median (inter-quartile range (Q1-Q3))	72.65 (18.13 to 251.7)	75.75 (18.63 to 255.0)		

Statistical analyses

Statistical analysis title	Serological response dsDNA (continuous variables)
Comparison groups	Low-dose IL-2 v Analysis population
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5566
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.17
upper limit	140.7
Variability estimate	Standard deviation
Dispersion value	136.9

Secondary: Corticosteroid dose
End point title: Corticosteroid dose
End point description: Change from baseline in the daily dose of corticosteroids at day 62
End point type: Secondary
End point timeframe: day 1 to day 62

End point values	Low-dose IL-2	Analysis population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: mg/day				
median (inter-quartile range (Q1-Q3))	7.5 (5 to 11.25)	7.5 (5 to 13.75)		

Statistical analyses

Statistical analysis title	Corticosteroid dose (continuous variables)
Comparison groups	Low-dose IL-2 v Analysis population
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.625
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.169
upper limit	6.669
Variability estimate	Standard deviation
Dispersion value	6.877

Adverse events

Adverse events information

Timeframe for reporting adverse events:

31.03.2014-20.10.2016
up to 22 weeks for each participant (including screening and follow-up periods)

Adverse event reporting additional description:

Safety assessments were performed at every scheduled and unscheduled study visit during the whole study period and included a complete physical examination with vital signs, current history and symptoms, changes in concomitant medications, assessment of adverse events (AE) and safety laboratroy tests.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Safety population

Reporting group description:

Safety and tolerability were evaluated descriptively in patients who received at least one dose of aldesleukin (safety population). Safety assessments were performed at every scheduled and unscheduled study visit during the whole study period and included a complete physical examination of all relevant body systems with vital signs (axillary body temperature, pulse rate in resting position, systolic and diastolic blood pressure in resting position), a complete assessment of current history and symptoms, changes in concomitant medications, assessment of adverse events (AE) and safety laboratory test.
Any AE occurring after the screening visit was recorded and assessed according to incidence, frequency, duration, severity, toxicity grade and causal relationship to the study medication.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Peripheral ischemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Skin infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	7		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	10 / 10 (100.00%)		
occurrences (all)	32		
Fever			
subjects affected / exposed	7 / 10 (70.00%)		
occurrences (all)	15		
Chills			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	6 / 10 (60.00%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2015	Change of principal investigator and his deputy.

Notes:

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.

- Single-arm study without active comparator
- Small number of enrolled subjects (n=10)

Notes: