CHARITÉ

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Medizinische Klinik mit Schwerpunkt Rheumatologie und Klinische Immunologie
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Unser Zeichen: JH

Berlin, 26.11.2019

Ergebnisbericht für klinische Prüfungen gemäß § 42b AMG

Titel der Studie:	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
Kurztitel der Studie:	PRO-IMMUN
Sponsor:	Charité – Universitätsmedizin Berlin
Leiter der klinischen Prüfung:	Prof. Dr. med. Gerd-Rüdiger Burmester Dr. med. Jens Humrich (Stellvertreter) Medizinische Klinik mit Schwerpunkt Rheumatologie und Klinische Immunologie, CC12, CCM Charitéplatz 1, 10117 Berlin Tel.: +49 (0)30 450 513 061 Fax: +49 (0)30 450 513 917 Email: gerd.burmester@charite.de
EudraCT-Nr.:	**2013-001599-40**
Prüfplan-Code:	**23032013**
Aktuelle Protokollversion:	**Version 1.04**

Name des IMP:	**Aldesleukin (rekombinantes humanes Interleukin-2)**
Studiendesign:	**Offene, unkontrollierte, monozentrische Phase I/IIa Studie**
Datum der Genehmigung durch das BfArM	**03.01.2014**
Datum der zustimmenden Bewertung durch die zuständige Ethik-Kommission	**09.12.2013**
Datum der zustimmenden Bewertung einer nachträglichen Änderung durch die Ethik-Kommission	**17.02.2014**
Datum der zustimmenden Bewertung einer nachträglichen Änderung durch das BfArM (Amendment A01)	**21.05.2015**
Datum der zustimmenden Bewertung einer nachträglichen Änderung durch die Ethik-Kommission (Amendment A01)	**22.05.2015**
Beginn der klinischen Prüfung:	**31.03.2014**
Berichts-Zeitraum:	**31.03.2014 bis 20.10.2016**
Geplante Fallzahl:	**12 inklusive 2 zurückgezogene Teilnehmer**
Ende der klinischen Prüfung:	**19.10.2018**
Rekrutierungen:	**10**
Regulär beendete Fälle:	**9**
Noch eingeschlossene Teilnehmer:	**0**
Zurückgezogene Teilnehmer:	**1**
Anzahl der Fälle dieses Berichts:	**10**
Datum der Mitteilung über die Beendigung der klinischen Prüfung	**07.12.2018**
Datum des Berichts	**26.11.2019**

FINAL REPORT

1. SPONSOR

Charité - Universitätsmedizin Berlin

Charitéplatz 1

10117 Berlin, Germany

2. NAME OF FINISHED PRODUCT:

Proleukin

3. NAME OF ACTIVE SUBSTANCE

Aldesleukin (recombinant human interleukin-2)

4. INDIVIDUAL STUDY TABLE

Not applicable

5. TITLE OF STUDY

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)

6. PRINCIPAL INVESTIGATORS

Prof. Dr. med. Gerd-Rüdiger Burmester (Principal Investigator)

Dr. med. Jens Humrich (Deputy Principal Investigator)

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7. STUDY CENTRE

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8. PUBLICATION

The manuscript containing all relevant data and information referring to the trial including the outcomes of the primary and secondary endpoints, all relevant safety analyses, dose-response analyses, study procedures and methods, statistical analyses, relevant figures and tables of analysed parameters and the discussion with conclusions, was published on September 1st 2019 as a full research article in *The Lancet Rheumatology:*

Humrich JY, von Spee-Mayer C, Siegert E, Bertolo M, Rose A, Abdirama D, Enghard P, Stuhlmüller B, Sawitzki B, Huscher D, Hiepe F, Alexander T, Feist E, Radbruch A, Burmester GR, Riemekasten G. Low-dose interleukin-2 therapy in refractory systemic lupus erythematosus: an investigator-initiated, single-centre phase 1 and 2a clinical trial. ***Lancet Rheumatol.*** **2019;1(1):e44-e54.**

The published manuscript also contains data from two patients who were treated with the study regimen in a compassionate use setting before the clinical trial was started. These patients met the eligibility criteria of the trial and were analyzed and followed up with similar procedures as described in the protocol. The **abstract** of the manuscript is provided below:

Background

An acquired deficiency of interleukin-2 (IL-2) and related defects in regulatory T cell homeostasis are thought to play a crucial role in the pathogenesis of systemic lupus erythematosus. We hypothesised that reconstitution of regulatory T-cell homoeostasis with low doses of IL-2 would be beneficial to patients with systemic lupus erythematosus.

Methods

In this uncontrolled, phase 1 and 2a trial done in the Department of Rheumatology and Clinical Immunology at Charité-University Medicine Berlin (Berlin, Germany), we assessed the safety and tolerability of low-dose recombinant human IL-2 (aldesleukin) and its effects on regulatory T cells. We recruited patients aged 18-75 years with a confirmed diagnosis of systemic lupus erythematosus and moderate-to-severe disease activity despite previous treatment with at least two conventional therapies. Patients were given four cycles of low-dose aldesleukin daily for 5 days followed by a 9-16 day rest. The primary endpoints were safety and the number of patients who achieved at least a 100% increase in the proportion of CD25hi-expressing cells among circulating CD3+CD4+FOXP3+CD127lo regulatory T cells at day 62 (ie, after four treatment cycles). Secondary endpoints included disease activity as measured by the Safety of Estrogens in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) and the British Isles Lupus Assessment Group (BILAG) score, disease flares as measured by the SLEDAI flare index, auto-antibody and complement concentrations at day 62. Exploratory endpoints included various cellular and immunological parameters. The trial is registered with WHO/ICTRP, number DRKS00004858.

Findings

Between March 31, 2014, and May 27, 2016, 13 patients were screened, of whom ten met eligibility criteria and were enrolled in the trial. Two additional patients were treated between April 1, 2013, and March 11, 2014, in a compassionate use setting. Eleven (92%) of the 12 patients achieved the primary endpoint. 159 adverse events were recorded, 75 (47%) of which were treatment related. Most treatment-related adverse events were transient and

mild to moderate (grade 1–2). The most common adverse event was injection-site reaction (20%). No serious adverse events occurred during the treatment period. In ten (83%) of 12 patients, SELENA-SLEDAI scores were lower at day 62 than at baseline, and no severe disease flares were observed during the treatment period. Decreased disease activity correlated with the magnitude of increase in the proportion of activated regulatory T cells. IL-2 treatment resulted in a preferential proliferation of regulatory T cells that retained suppressive capacity. We observed decreases in cells that are involved in the regulation of germinal-centre reactions.

Interpretation

Low-dose IL-2 therapy is safe and well tolerated and selectively promotes the expansion of functional regulatory T cells in patients with moderate-to-severe systemic lupus erythematosus. Low-dose IL-2 treatment might also be beneficial in reducing disease activity, although larger trials are needed to address efficacy.

Funding

German Research Foundation (DFG).

9. STUDIED PERIOD

Date of first enrolment:	31.03.2014
Date of last visit last patient (LVLP):	20.10.2016
Date of end of clinical trial including completion of data analysis and data collection	19.10.2018

10. PHASE OF DEVELOPMENT

Prospective, open-label, uncontrolled, single-centre phase 1 and 2a clinical trial

11. OBJECTIVES

Primary Objective

The primary objective of PRO-IMMUN was to evaluate the safety and tolerability of a repetitive and cyclic subcutaneous low-dose regimen with the recombinant human interleukin-2 analogue aldesleukin (Proleukin®) and its effects on the Treg population 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 AE at every scheduled visit after the screening visit (Visits 2-11) and at every unscheduled visit.

Secondary Objectives

The secondary objectives of PRO-IMMUN were to evaluate the clinical efficacy of low-dose IL-2 therapy by assessment of the following serological and clinical response parameters:

- Changes in serum antibody titers for anti-dsDNA-Abs determined by ELISA and by the Crithidia luciliae IFT, serum levels of the complement factors C3 and C4 and serum levels of circulating immune complexes at week 9 (Visit 9) compared to baseline at week 1 (Visit 2). Exploratory assessments include changes in values before and one day after each therapeutic cycle (Visits 3-9; weeks 1, 3, 6, 9), and at follow-up and termination visits (Visits 10 and 11; week 12 and 18) compared to baseline values (Visit 2; week 1) and compared to previous values obtained throughout the study.
- Changes in serum antibody titers for ANA, ENA, anti-SmD1-Abs and other individually relevant serological markers, which were present at baseline or at previous examinations, at week 9 (Visit 9) compared to baseline at week 1 (Visit 2). Exploratory assessments include changes in values one day after the 2nd cycle (Visit 5; week 3) and at follow-up and termination visits (Visits 10 and 11; weeks 12, 18) compared to baseline values (Visit 2; week 1) and compared to previous values obtained throughout the study.
- Changes in the disease activity scores SELENA-SLEDAI and BILAG 2004, and changes in PGA and VAS at week 9 (Visit 9) compared to baseline at week 1 (Visit 2). Exploratory assessments include changes in values before and one day after each therapeutic cycle (Visits 3-9; weeks 1, 3, 6, 9), and at follow-up and termination visits (Visits 10 and 11; week 12 and 18) compared to baseline values (Visit 2; week 1) and compared to previous values obtained throughout the study.
- Changes in health related Quality of Life (SF36®) one day after the 4th therapeutic cycle (Visit 9; week 9) compared to baseline values (Visit 2; week 1). Exploratory assessments include changes in values at follow-up and termination visits (Visits 10 and 11; week 12 and 18) compared to baseline values (Visit 2; week 1) and compared to previous values obtained throughout the study.
- Changes in organ specific parameters based on individual SLE manifestations either at week 9 (Visit 9) and/or during the follow-up period (weeks 12-18) compared to values obtained at the baseline visit (Visit 2; week 1) or during the screening period and exploratory, if available, also compared to previous values obtained throughout the study.
- Changes in SLE-associated organ damage by the SLICC/ACR Damage Index one day after the 4th cycle (visit 9; week 9) and at the termination visit (Visit 11; week 18) compared to values at screening visit (Visit 1).
- Assessment of the durability of clinical and serological responses in subjects who responded to the therapy by comparing values at the follow-up and termination visits

(Visits 10 and 11; week 12 and 18) to values from week 9 (Visit 9) and to baseline values (Visit 2; week 1).

- Assessment of incidence, frequency and severity of SLE flares throughout the whole study.

Exploratory objectives (accessory scientific assessments)

The exploratory objectives of PRO-IMMUN were to evaluate the immunological and cellular responses induced by low-dose IL-2 therapy (not reported here, see Humrich et al. *Lancet Rheumatol.* 2019, for details)

(see also APPENDIX 1.1-1.3 for study flow chart and schedule of study assessments).

12. METHODOLOGY

PRO-IMMUN is a combined phase 1 and 2a, interventional, prospective, open-label, uncontrolled, single-centre and investigator-initiated trial addressing the safety, tolerability, efficacy and immunological responses of a subcutaneous low-dose regimen with 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. Patients were given four cycles of low-dose aldesleukin daily for 5 days followed by a 9-16 day rest. There was no placebo-controlled group. Study patients continued to receive the best available concomitant standard-of-care SLE medications, which did not interfere with the study medication. The primary endpoints were safety and the number of patients who achieved at least a 100% increase in the proportion of CD25hi-expressing cells among circulating CD3+CD4+FoxP3+CD127lo regulatory T cells at day 62 after four treatment cycles compared with baseline at day 1. Secondary endpoints included changes in disease activity as measured by the Safety of Estrogens in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) and the British Isles Lupus Assessment Group (BILAG) score, disease flares as measured by the SLEDAI flare index, and auto-antibody and complement concentrations at day 62 compared with baseline at day 1. Exploratory endpoints included various cellular and immunological parameters.

13. NUMBER OF PATIENTS

Planned: 10 (+2 potential replacements for drop-outs)

Analysed: 10 including 1 drop-out

14. DIAGNOSIS AND ELIGIBILITY CRITERIA

Diagnosis / Study population:

The study population consisted of patients aged 18-75 years with a confirmed diagnosis of **Systemic Lupus Erythematosus (SLE)** according to the American College of Rheumatology (ACR) criteria (fulfilling ≥ 4 criteria) and a moderate-to-severe disease

activity (SELENA-SLEDAI ≥ 6) despite previous treatment with at least two different conventional therapies.

CRITERIA FOR INCLUSION

1. Patients with diagnosis of SLE made and documented by the investigator according to the revised ACR (1997) criteria fulfilling ≥ 4 criteria with at least one autoantibody level abnormal (ANA, anti-dsDNA-abs, anti-Sm-abs, anti-Phospholipid-abs).
2. Active SLE patients with a SELENA-SLEDAI ≥ 6 despite previous treatment with at least two different standard immunosuppressive or immunomodulatory therapies.
3. An EC approved written informed consent form signed and dated by the patient must be obtained prior to the performance of any protocol procedures and prior to the administration of the study medication (according to AMG §40 (1) 3b).
4. Stable dosage of standard immunosuppressive or immunomodulatory treatments for at least 4 weeks prior to the first administration of the study medication.
5. Daily dose of glucocorticosteroids must be ≤ 30mg prednisolone (or equivalent) at the day of baseline visit (Visit 2).
6. Age of patients >18 years and ≤ 75 years.
7. Willingness to perform blood analyses and to discontinue therapies which potentially interfere with the study medication.
8. Female patients of childbearing potential must have a negative serological pregnancy test at the screening visit (Visit 1).
9. Female patients of childbearing potential must use at least two reliable methods of birth control (1 of which is a barrier method) during study participation and up to 3 months after completion of the last (4^{th}) treatment cycle.
10. Male patients must agree to use a contraceptive barrier method (eg, condom) with adjunct spermicide during sexual intercourse from the time of the administration of the study medication until at least 3 month after completion of the last (4^{th}) treatment cycle.

CRITERIA FOR EXCLUSION

1. Hypersensibility to aldesleukin or its excipients.
2. Patients with a reduced general condition of 2 or more according to the ECOG (Eastern Cooperative Oncology Group) Performance Status.
3. Severe impairment of vital organ or life-threatening disease.
4. Thrombocytopenia with platelet count of <100.000/µl.
5. Leukocytopenia with WBC of <3.000/µl or neutropenia with a neutrophil count of <1.500/µl.
6. Anemia with hemoglobin of <9.0 g/dl.
7. History of thrombotic microangiopathy (TTP).

8. History of thrombosis or thrombotic event (including venous thrombosis, pulmonary embolism, cortical sinus thrombosis, stroke, or arterial embolism causing digital gangrene or tissue necrosis) within the last 6 month prior to the screening visit (Visit 1).
9. Infection requiring antibiotic therapy or infection requiring hospitalisation within the last 4 weeks prior to the baseline visit (Visit 2).
10. Long-term chronically active infectious disease, HIV infection (positive serum antibodies against HIV1/2), active or chronic hepatitis B infection (positive for HBs-Ag in serum), active or chronic hepatitis C infection (positive for serum antibodies against HCV), active tuberculosis.
11. Pleuritis with pleural effusion of clinical relevance (≥ grade 2; CTCAE v4.03).
12. Pericarditis with pericardial effusion of clinical relevance (≥ grade 3; CTCAE v4.03).
13. Chronic or acute renal impairment with an eGFR of < 30 ml/min/1·73 m^2 (calculated GFR using the MDRD formula with modification for race) or oliguria.
14. Severe impairment of liver function with elevated plasma levels of bilirubin of ≥ 2 mg/dl or an INR of ≥ 1.7.
15. Patients with diagnosis of type-1 diabetes mellitus or of Crohn´s Disease.
16. Patients with inadequately controlled type-2 diabetes mellitus (HbA1c >9%) or patients with type-2 diabetes mellitus and history of recurrent hyperglycemia or hypoglycemia of clinical relevance (≥ grade 3 according to the CTCAE v4.03).
17. Patients who received allogeneic solid organ transplants, except patients who underwent an autologous or allogeneic hematopoetic stem-cell transplantation (HSCT) more than two years prior to the screening visit (Visit 1) and who did not develop graft-versus-host disease (GvHD).
18. Patients with diagnosis of malignant neoplasm or treatment for malignant neoplasm within the last 5 years prior to the screening visit (Visit 1), except adequately treated basal cell carcinoma or squamous cell carcinoma of the skin and carcinoma in situ of the uterine cervix.
19. Patients with severe impairment of pulmonary function: severe restrictive lung disease with FVC of <50% of predicted value or obstructive lung disease with FEV_1 of <50% of predicted value or O_2-saturation of <90% determined by a pulse oxymeter under room air and in resting position.
20. Severe cardiomyopathy or chronic heart failure with an ejection fraction of <30% or of ≥ grade 3 according to the CTCAE v4.03; instable angina pectoris; coronary heart disease with previous stent implantation within the last 3 month prior to the screening visit (Visit 1) or with three-vessel involvement; cardiac intervention or myocardial infarction within the last 12 month prior to the screening visit (Visit1); history of cardiac arrest.

21. Cardiac arrhythmias of clinical relevance or requiring permanent treatment (≥ grade 2 according to the CTCAE v4.03); persistent or permanent atrial fibrillation; disturbance of transmission of impulses of clinical relevance (AV-Block >1°).
22. Valvular heart disease of clinical relevance (≥ grade 3 according to the CTCAE v4.03).
23. Patients with inadequately controlled permanently abnormal heart rate with <45 or >120 beats per minute in resting position.
24. Patients with inadequately controlled permanent hypotension with systolic blood pressure <100 mmHG or diastolic blood pressure <50 mmHG in resting position.
25. Patients with inadequately controlled permanent hypertension with systolic blood pressure >160 mmHG or diastolic blood pressure >100 mmHG in resting position
26. History of orthostatic dysregulation, fainting, or blackouts within the last 3 month prior to the screening visit (Visit 1).
27. History of chronic organic psychosis or endogenous psychosis (schizophrenia, mania, bipolar disorder), except mild and transient forms of depression.
28. History of seizures within the last 6 month prior to the screening visit (Visit 1).
29. Treatment with Rituximab or any B cell depleting therapy within the last 6 months prior to the screening visit (Visit 1).
30. Treatment with calcineurin-inhibitors (ciclosporin A, sirolimus, tacrolimus), cyclophosphamide, methotrexate (MTX) or Belimumab within the last 4 weeks prior to the baseline visit (Visit 2).
31. Treatment with antiproliferative, cytostatic or cytotoxic agents within the last 4 weeks prior to the baseline visit (Visit 2) with the exception of permitted concomitant SLE-related medications.
32. Treatment with alpha and beta-interferons within the last 4 weeks prior to the baseline visit (Visit 2).
33. Experimental therapy or participation in another clinical study with investigational medicinal products within the last three month prior to the baseline visit (Visit 2).
34. Necessity for application of radiographic iodinated contrast media during and 2 weeks after the completion of the last (4^{th}) treatment cycle.
35. Live vaccination within the last 4 weeks prior to the baseline visit (Visit 2), or plan to receive a live vaccine during study participation.
36. Major surgery within the last 4 weeks prior to the screening visit (Visit 1) or plan to have elective major surgery during study participation.
37. Pregnancy and lactating women.
38. Lack of ability or willingness to practice reliable methods of contraception during the study (female and male participants).
39. Abuse of alcohol or drugs.

40. Lack of willingness for storage and transmission of pseudonymized medical data obtained during the clinical study.
41. Minors and subjects who are incapable to provide informed consent or who are considered to be incapable of adhering to the protocol and visit schedule and to be unable to comply with all study requirements according to the judgment of the Investigator (according to AMG § 42(2) and (3)).
42. Subjects kept in detention due to judicial or official order (according to AMG § 40 (1) 4).

15. TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

TEST PRODUCT:

Generic name: Aldesleukin, Interleukin-2
Brand name: Proleukin®
Producer/Supplier: Novartis Pharma GmbH, 90327 Nürnberg, Germany
Pharmacotherapeutic Group: Immunostimulators, immunomodulators, cytokines, interleukin-2
ATC-Code: L03A C01

BATCH NUMBERs:

The following batches of the test product (aldesleukin) were used in this study:

DA.1522-AL; 40.1010-1E; 40.7682-L; 50.2519-R

DOSE AND MODE OF ADMINISTRATION:

Therapeutic regimen and intended dose escalations:

The therapeutic regimen consisted of four separate treatment cycles each with daily subcutaneous injections 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. In the 1st treatment cycle all patients were planned to received 1.5 million IU of aldesleukin (Proleukin®) per day for five consecutive days (days 1-5, week 1) followed by a washout period of nine days. In the 2nd treatment cycle (days 15-19, week 3), patients, who did not fulfil any dose reduction criteria (see below) could receive 3.0 million IU of aldesleukin per day for five consecutive days followed by a 16-day washout period. In the 3rd (days 36-40, week 6) and 4th cycle (days 57-61, week 9), patients, who did not fulfil any dose reduction criteria with the daily dose of 3.0 million IU, a maximum aldesleukin dose of 4.5 million IU per day was intended to be administered for five consecutive days with a washout period of 16 days in between (see also APPENDIX 1.2 for details on Study and Treatment Schedule). In each treatment cycle, investigators either delivered the first dose or supervised the patient self-injecting at our site. The remaining four injections were given to patients as pre-filled syringes in a cooling box after appropriate instruction by investigators.

Dose adaptions:

Dose adaptations during the treatment period were applied 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.

Dose adaption and discontinuation criteria:

Criteria for reduction of daily dose in subsequent cycle:

A reduction of the single daily dose in the subsequent treatment cycle from 1.5 million IU of aldesleukin per day to 0.75 million IU per day, or from 3.0 million IU of aldesleukin per day to 1.5 million IU of aldesleukin per day, or from 4.5 million IU per day to 3.0 million per day was done if one of the following dose reduction criteria was fulfilled in the previous treatment cycle:

- The percentage of FoxP3+CD127lo Treg among CD3+CD4+ T cells exceeds 50% in total.
- Increase in plasma creatinine of > 25% above normal range or worsening of pre-existing renal insufficiency with increase in plasma creatinine of > 25 % of previously elevated value or new onset of oliguria.
- Increase in plasma levels of liver transaminases (GOT, GPT) of >50% of normal range, increase in levels of plasma bilirubin of >25 % above normal range.
- New onset of anemia with blood hemoglobin of <10·0 g/dl or worsening of pre-existing anemia with blood hemoglobin of <8·0 g/dl or decrease in blood hemoglobin of >20% of the previous value.
- Leukocytopenia with WBC of <2.500/µl or neutropenia with a neutrophil count of <1.250/µl.
- Eosinophilia with an eosinophil count of >25% above the normal range.
- Lymphopenia with lymphocyte count of <400/µl.
- New onset of thrombocytopenia with platelet count of <100.000/µl or worsening of pre-existing thrombocytopenia with platelet count of <75.000/µl.
- Increase in numbers of circulating NK cells of >50% above normal range.
- Increase in numbers of circulating monocytes of >50% above normal range.
- Increase in levels of plasma fibrinogen of >25% above the normal range.
- Inadequately controlled permanently abnormal heart rate with <45 or >120 beats per minute in resting position.
- Inadequately controlled permanent hypotension with systolic blood pressure <100 mmHG or diastolic blood pressure <50 mmHG in resting position.

- Inadequately controlled permanent hypertension with systolic blood pressure >160 mmHG or diastolic blood pressure >100 mmHG in resting position.
- New onset or worsening of pre-existing dyspnea, cough or chest pain (CTCAE grade 2 or higher).
- New onset or worsening of pre-existing vertigo, headache, paresthesia, dizziness or somnolence (CTCAE grade 2 or higher).
- New onset or worsening of pre-existing nausea, vomiting, diarrhea or stomatitis (CTCAE grade 2 or higher).
- Development of limb edema (CTCAE grade 3 or higher).
- Severe injection site reaction (CTCAE grade 3 or higher)
- Any AE or abnormal laboratory finding not listed above, that is not due to SLE activity and that in the judgement of the investigator requires a dose reduction of the study medication. As a general guideline, AEs in relevant organ systems of ≥ grade 2 according to the CTCAE (version 4.03) can be considered a reason for a dose reduction. However, exceptions to this guideline apply for certain AEs and certain circumstances. In this case, the investigator will discuss further actions with the Principal Investigator.

Criteria for maintenance of daily dose in subsequent cycle:

The single daily dose in the subsequent treatment cycle was maintained at the same dose as in the previous treatment cycle if none of the dose reduction criteria was fulfilled and if the single dose in the previous cycle already was a reduced dose, which was administered for the first time in the previous cycle.

Criteria for increase of daily dose in subsequent cycle:

The single daily dose was increased from 0.75 million IU to 1.5 million IU of aldesleukin per day, or from 1.5 million IU to 3.0 million IU of aldesleukin per day, or from 3.0 million IU to 4.5 million IU of aldesleukin per day if none of the dose reduction criteria was fulfilled or if none of the dose reduction criteria was fulfilled and if the single daily dose in the previous cycle already was a reduced dose, which was administered for the second time in the previous cycle.

Criteria for discontinuation of the study medication:

- Development of a condition during the study that violates the inclusion/exclusion criteria with the exception of development of exclusion criteria that will lead to a dose reduction of the study medication (Exclusion criteria: 4, 5, 6, 23, 24, 25).
- Subject has thrombocytopenia with a platelet count of <50.000/µl.
- Subject has leukocytopenia with a leukocyte count of <2.000/µl or neutropenia with a neutrophil count of <1000/µl.
- Occurrence of a severe AE or of an abnormal laboratory finding that in the judgement of the investigator requires a discontinuation of the study medication.

- Occurrence of an AE that meets the criteria for an SAE or is classified as an AE grade 4 according to the CTCAE criteria (version 4.03).
- Development of a severe flare according to the definitions of the SELENA-SLEDAI Flare Index (SRI) during the treatment period (Visits 2-9).
- Requirement for treatment with any of the prohibited concomitant medications during the treatment period (Visits 2-9).
- Occurrence of an allergic reaction to Aldesleukin or its excipients that will lead to interference with the protocol treatment.
- Pregnancy, as evidenced by a positive serological pregnancy test.
- Subject has an infection that requires i.v. antimicrobial treatment, which timely interferes with the scheduled treatment cycles.
- Subject is non-complaint with protocol procedures or the study medication.
- Subject receives less than 4 single doses in a treatment cycle due to any reason.
- Investigator determines that it is in the best interest of the subject to discontinue the study medication.
- Subject is lost to follow-up

Conducted dose adaptions during the treatment period:

All 10 enrolled patients initially received a single daily dose of 1.5 million IU of aldesleukin per day for five consecutive days (cumulative dose of 7.5 million IU) during the 1st treatment cycle as scheduled. After a wash-out period of nine days, seven of the 10 patients were eligible to receive an increased daily dose of 3.0 million IU (cumulative dose of 15.0 million IU) in the 2nd treatment cycle. Three patients fulfilled one dose reduction criterion in the 1st cycle, i.e. lymphopenia (grade 3) and increase in fibrinogen (grade 2), and therefore received a reduced daily dose of 0.75 million IU of aldesleukin (cumulative dose of 3.75 million IU) in the consecutive 2nd cycle. After another 16-day wash-out period, the daily dose in the 3rd cycle was reduced again to 1.5 million IU in all of the seven patients who received 3.0 million IU in the 2nd cycle because of fulfilment of one or more of the following dose reduction criteria, i.e. fever (grade 1-2), chills (grade 1), arthralgia and myalgia (grade 1), flu-like symptoms (grade 2), injection site reaction (grade 2), dizziness (grade 2), fatigue (grade 2), headache (grade 3), nausea (grade 2), increase in fibrinogen (grade 2), and %FoxP3+CD127lo Treg among CD3+CD4+ T cells > 50%. Four of these seven patients were also maintained on 1.5 million IU during the 4th treatment cycle. Three of these seven patients received a reduced daily dose of 0.75 million IU in the 4th treatment cycle due to fulfilment of one dose reduction criterion in the 3rd cycle, i.e. leukopenia (grade 2), eosinophilia (grade 1), and injection site reaction (grade 2). Two of the three patients who received a reduced dose of 0.75 million IU already in the 2nd cycle were maintained on this dose also in the 3rd cycle. Their daily dose was increased again to 1.5 million IU in the 4th cycle because of absence of dose reduction criteria during the 3rd cycle. The other patient who received a reduced dose of 0.75 million IU in the 2nd cycle (patient DD) had to discontinue the treatment after the 2nd cycle due to repeated fulfilment of dose reduction criteria (1st time: lymphopenia, 2nd time: increase in fibrinogen). None of the patients was eligible to receive the intended daily dose of 4.5 million IU of aldesleukin in the 3rd and 4th

treatment cycle. In five patients, who developed relevant adverse events and discomforts within a treatment cycle, only four of the five injections per cycle or one of the five injections in a reduced dose was delivered (cumulative doses of 6.0, 6.75 and 12.0 million IU per cycle).

16. DURATION OF TREATMENT

Screening period:	up to 4 weeks
Treatment period:	9 weeks
Follow-up period:	9 weeks
Total individual duration of study:	max. 22 weeks

17. REFERENCE THERAPY

Not applicable, no placebo or active comparator was used in this uncontrolled study.

18. CRITERIA FOR EVALUATION: EFFICACY; SAFETY

EFFICACY ASSESSMENTS

1. Cellular efficacy / Treg response

The primary objective of this study was to evaluate the response of the Treg population to low-dose IL-2 therapy after four treatment cycles by using flow cytometry.

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)

2. Clinical Efficacy

Clinical efficacy (secondary endpoints) was evaluated by assessment of the changes in the following disease activity scores and measures at day 62 (week 9; after four treatment cycles) in comparison to baseline at day 1 (before the 1st treatment cycle):

- Safety of Estrogens in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)
- British Isles Lupus Assessment Group (BILAG) 2004 score
- SLEDAI flare index
- Physician´s global assessment (PGA)
- Patient´s visual analogue score (VAS)

- Systemic Lupus International Collaborating Clinics / American College of Rheumatology-Damage Index (SLICC/ACR-DI)
- Serum antibody titers for anti-dsDNA-Abs and other individually relevant auto-antibodies
- Serum levels of the complement factors C3 and C4 and serum levels of circulating immune complexes

SAFETY ASSESMENTS

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 and assessment of adverse events (AE).

Any AE occurring after the screening visit was recorded and assessed. We followed the International Council for Harmonisation's Good Clinical Practice (ICH-GCP) guidelines and used the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) at each study visit to assess AEs according to incidence, frequency, duration, severity, toxicity grade and causal relationship to the study medication. The tolerability was evaluated by comparing the frequency and severity of AEs and of safety laboratory deviations between the administered doses per treatment cycle. To avoid a potentially excessive immunosuppression, an increase in the percentage of FoxP3+CD127lo Treg among CD3+CD4+ T cells above 50% was defined as a dose reduction criterion, but such an event was not recorded as an AE.

Safety laboratory tests were performed at every study visit and included a complete blood count, C-reactive protein (CRP), creatinine, bilirubine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (gGT), lipase, ferritin, haptoglobin, cholesterol, lactate dehydrogenase (LDH), creatine kinase (CK), N-terminal prohormone of brain natriuretic peptide (NTproBNP), thyreoidea-stimulating hormone (TSH), quick, partial thromboplastin time (pTT), fibrinogen, factor VIII, D-dimers, soluble CD25 (sIL-2R), and urine analyses (dip stick and protein concentrations). Serum-electrophoresis, IgG, IgA, IgM, and ß2-mikroglobulin were analysed at baseline, day 20, day 62, day 83 and day 120.

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.

19. STATISTICAL METHODS

Statistical analysis for all endpoints was performed with GraphPad Prism version 7.02 (GraphPad Software Inc., La Jolla, USA). For the primary endpoint analysis and for all secondary and exploratory endpoints, the two-sided Wilcoxon signed-rank test was used for paired comparisons of changes between baseline (day 1, week 1) and day 62 (week 9, after the 4th treatment cycle). The two-sided Wilcoxon signed-rank test was also used for paired comparisons of changes within each of the treatment cycles (day 1 vs day 6; day 15 vs day 20; day 36 vs day 41; day 57 vs day 62) and of changes between baseline and days 6, 15, 20, 36, 41, 57, 83, and 120. 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. All patients who received at least one dose of aldesleukin were included in the safety population. The Mann-Whitney test was used to analyse for differences in immunological parameters between clinical responders and non-responders. Patients were classified as clinical responder if at least one clinical manifestation had disappeared at day 62 according to the definitions of the SELENA-SLEDAI. Patients showing only normalization in any of the laboratory items of the SELENA-SLEDAI such as complement, dsDNA-abs, or cytopenia were not classified as clinical responder. Correlations and dose-response analyses were done with non-parametric Spearman's rank correlation coefficients. Differences were considered significant if p-values were less than 0·05.

20. SUMMARY

EFFICACY RESULTS

All 12 treated patients, including the 10 patients enrolled in the trial and the two compassionate use patients, showed cycle- and dose-dependent increases in the proportions and numbers of CD25hi-expressing cells among the CD3+CD4+FoxP3+CD127lo Treg population and 11 patients achieved the primary endpoint (p=0.0005). No relevant or persistent increases in numbers of other lymphocyte subsets were observable. Ten patients showed a reduction in SELENA-SLEDAI (p=0.0103) and eight patients achieved a clinical response with a disappearance of clinical manifestations such as rash, arthritis, myositis, mucosal ulcers and alopecia. Levels of the complement factor C3 were significantly increased at day 62 compared with baseline (p=0.0078). No reduction in levels of anti-dsDNA-Abs or of other relevant autoantibodies was observed (see APPENDIX 2.1 and 2.2 for statistical analysis and individual changes in clinical parameters). The decrease in SELENA-SLEDAI correlated with the magnitude of increase in the proportions of CD25hi-expressing Treg (r=0.6722; p=0.0199). Low-dose IL-2 therapy also preferentially augmented the proliferation of Treg resulting in a partial restoration of the homeostatic balance between Treg and conventional T cells. The IL-2 expanded Treg population displayed a preserved suppressive capacity and expressed high levels of the Treg-associated molecules Helios, CD39 and CD137. Concomitantly, we observed decreases in cells that are involved in the regulation of germinal-centre reactions.

SAFETY RESULTS

In the complete reporting period of this clinical trial, **159 adverse events (AEs)** were recorded in the trial population (n=10) (APPENDIX 3.1 and 3.4), including **5 serious adverse events (SAE)** (APPENDIX 3.2) and **7 relevant abnormal laboratory findings** (APPENDIX 3.3), which led to reduction of the daily dose in the subsequent treatment cycles and/or was classified as AE. This report includes data from 9 subjects who completed the trial by regular termination and from one subject who had to discontinue the study medication after 2 cycles of aldesleukin (Subject 04) due to relevant changes in laboratory parameters necessitating a repeated dose reduction of the study medication (lymphopenia, increase in fibrinogen). This patient was followed-up after discontinuation of the study medication until the termination visit in accordance with the protocol procedures. The patient was not replaced because the patient could be included in the efficacy analysis by last-observation-carried forward (LOCF) modality and because the primary objective of the study was already achieved.

Adverse events (AE)

The large majority of AEs was mild to moderate (CTCAE grade 1 or 2) and quickly resolved within several days during the wash-out periods. In nearly all patients treatment-related injection site reactions (mild erythema, grade 1-2) were observed independent of the applied dose, rendering this the most frequent AE in our study (20.1% of AEs). Other frequent AEs were fever (9.4%), myalgia (8.8%), chills (4.4%), and headache (4.4%), which could be easily managed with antipyretics. Infections accounted for 11.9% of all AEs, but none was treatment-related and most of them occurred during the follow-up phase (APPENDIX 3.1, 3.4 and 3.5).

Serious adverse events (SAE)

No serious infections or serious adverse event (SAE) occurred during the treatment period. During the follow-up period five SAEs due to hospitalizations were recorded. Three of these hospitalizations occurred in one single patient, who was classified a non-responder, and whose admission to the hospital was necessary for the management of infections (bronchial infection, repeated skin infections) most likely due to the required intensification of therapy by cyclophosphamide. The other two hospitalizations occurred in the patient who had to discontinue the treatment after two treatment cycles due to repeated fulfilment of dose reduction criteria. At the first time this patient was admitted for the management of peripheral ischemia with digital necrosis of the toe associated with Raynaud´s syndrome and at the second time because of a superinfection of the digital necrosis (APPENDIX 3.2). One of these SAEs (peripheral ischaemia in subject 04) was judged to be possibly related to treatment, whereas the other four SAEs were unrelated to treatment. No suspected unexpected serious adverse reaction (SUSAR) or fatal event occurred during the whole study time.

Abnormal laboratory findings (includes results from the two patients treated in a compassionate use setting before the start of the trial)

Transient and modest treatment-related increases in numbers of eosinophils and in the plasma concentrations of fibrinogen and D-Dimers were observed in most patients without any correlation to the cumulative dose per cycle. Relevant increases above the upper limit of normal in eosinophils (grade 1) and in fibrinogen (grade 2), which according to the dose reduction criteria necessitated a reduction of the daily dose in the subsequent cycle, were

observed in one (subject 06) and two patients (subjects 04 and 05), respectively (APPENDIX 3.3). We also noted moderate and transient treatment-related increases in C-reactive protein (CRP) concentrations in all 12 patients (11 of whom had CRP concentrations higher than the upper limit of normal after any of the four cycles), which weakly correlated with the cumulative dose per cycle (r=0.3134; p=0.0360), reflecting the induction of a moderate acute-phase reaction by low-dose IL-2 therapy. Consistent with this, also higher levels of the acute-phase proteins haptoglobin, α-1-globulin, α-2-globulin and β-globulin were observed at day 62 (after 4 treatment cycles) compared with baseline. At present, the clinical relevance of these findings is unclear and needs further clarification, although, apart from fever and flu-like symptoms, there was no meaningful clinical correlate or adverse event associated with these laboratory deviations. Clinically irrelevant and very modest, but statistically significant decreases in hemoglobin in 10 patients of which 5 remained above and 3 already were below the lower limit of normal (≥ 12 g/dL) at baseline (p=0.0068; max. decrease from baseline 13.7%), in leukocyte counts in 11 patients of which 2 transiently dropped below the lower limit of normal (≥ 3.9 cells/nL) (p=0.0010; max. decrease from baseline 51.3%), and in neutrophil counts in 10 patients of which all remained above the lower limit of normal (≥ 1.5 cells/nL) (p=0.0425; max. decrease from baseline 56,8%) were detectable at day 62 compared with baseline values. These changes were considered to be unrelated to the treatment. In one patient (subject 03) the leukocyte count transiently decreased to 2.47 cells per nL (grade 2) after the 3rd treatment cycle which was judged to be possibly related to the treatment and led to a dose reduction in the subsequent cycle. In another patient (subject 01) the neutrophil count transiently decreased to 1.49 cells per nL (grade 2) in the follow-up period (unrelated). In two patients with pre-existing disease-associated lymphopenia (grade 3) (subjects 04 and 07), the lymphocyte count transiently decreased below 0.4 cells per nL after the 1st treatment cycle which was judged to be related to the disease itself and unrelated to the treatment but necessitated a dose reduction in the subsequent cycle according to the dose reduction criteria. In the other 10 patients no relevant changes in lymphocyte counts were observed during the treatment period until day 62 (p=0.6353). There were no relevant or significant changes in platelet counts, monocyte counts, liver enzymes, renal parameters, urine protein excretion, coagulation parameters, relevant plasma proteins and enzymes or levels of IgG, IgA, and IgM (APPENDIX 3.6). No relevant alterations in lung function tests, echocardiography, electrocardiogram (ECG) or abdominal ultrasound findings between the screening and the post-treatment phase were observed (APPENDIX 3.7).

Tolerability

Low-dose IL-2 therapy was well tolerated at daily doses of 0.75 and of 1.5 million IU of aldesleukin (cumulatively 3.75 and 7.5 million IU per cycle). In the eight patients, who received daily doses of 3.0 million IU of aldesleukin (cumulatively 15 million IU per cycle), a higher frequency and severity of AEs was observed (APPENDIX 3.5), particularly fever and chills (grade 1–2; four patients), influenza-like symptoms (grade 2; one patient), headaches (grade 3; one patient), dizziness (grade 2; one patient), and arthralgia and myalgia (grade 1; four patients). Accordingly, the daily dose of aldesleukin in all eight patients was reduced again to 1.5 million IU in the third treatment cycle. None of the patients was eligible to receive the scheduled maximum daily dose of 4.5 million IU of aldesleukin in the 3rd or 4th treatment cycle. According to these observations, the maximal well-tolerated dose of aldesleukin was 1.5 million IU of aldesleukin per day or cumulatively 7.5 million IU per cycle in this study.

Summary of safety data and final risk-benefit estimation:

In general, and after review of the published data, type, frequency, severity grade and duration of the observed adverse events in our clinical trial were very similar to those adverse events currently reported in the literature for low-dose interleukin-2 therapy with aldesleukin in patients with immune-mediated diseases including SLE (APPENDIX 4).

In conclusion, the benefits of low-dose IL-2 therapy for patients with refractory SLE by far outbalance the potential risks and discomforts of this treatment. According to the final safety data, we judge that this treatment has a very favorable risk-to-benefit ratio within a defined dose range.

21. FINAL CONCLUSIONS

This study demonstrates that low-dose IL-2 therapy is safe and well tolerated and is capable to promote the selective expansion of a functional Treg population in patients with moderate-to-severe SLE inadequately controlled by conventional therapies. Low-dose IL-2 treatment might also be beneficial in reducing disease activity, although larger and placebo-controlled trials are needed to address clinical efficacy. The concept of low-dose IL-2 therapy in SLE has emerged from pathophysiological findings and thus can be considered a novel targeted treatment option in SLE with a unique mode of action. The results of this trial provide important rationales and a profound scientific basis for more comprehensive and placebo-controlled clinical trials.

DATE OF REPORT: 26.11.2019

SIGNATURES:

Prof. Dr. med. Gerd-Rüdiger Burmester
Principal Investigator

Berlin, 02-DEC-2019
Place/Date

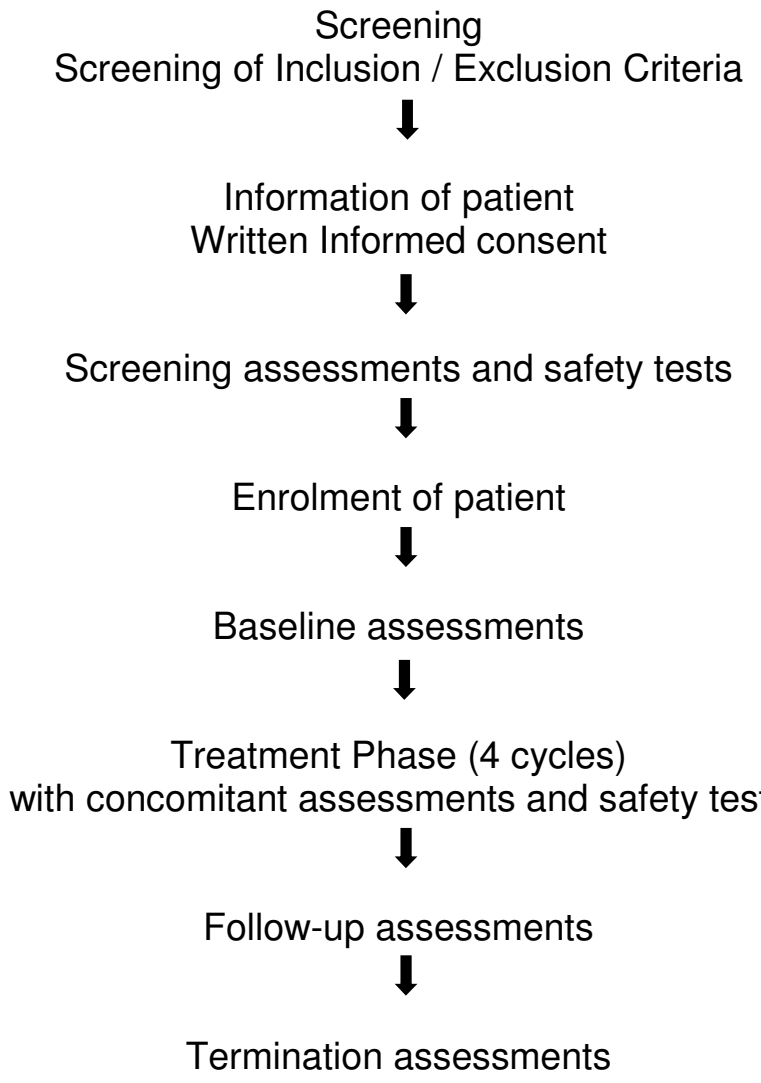
Dr. med. Jens Humrich
Deputy Principal Investigator
Study Coordinator

Lübeck, 26.11.2019
Place/Date

APPENDIX

1. STUDY DESIGN AND SCHEDULE OF ASSESSMENTS

1.1 Study Flow Chart



1.2 Study and Treatment Schedule

	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Follow-up	Termination
Visit	1	2 3	4 5	6 7	8 9	10	11
Week	-4 to -1	1	3	6	9	12	18
Day	-30 to -1	1 6	15 20	36 41	57 62	83 (+/-3)	120 (+/-5)
Single-dose		1.5 Mio IU	3.0 Mio IU	4.5 Mio IU	4.5 Mio IU		
Treatments							
Assessments							

3.3 Schedule of study procedures and assessments per visit

	Visit 1 Scree-ning	Visit 2 Base-line	daily during Cycle 1	Visit 3 after Cycle 1	Visit 4 before Cycle 2	Visit 5 after Cycle 2	Visit 6 before Cycle 3	Visit 7 after Cycle 3
Procedure	day-30 to day-1	day 0 week 1	day 1-5 week 1	day 6 week 1	day 15 week 3	day 20 week 3	day 36 week 6	day 41 week 6
Informed Consent	✓							
Demographic Data	✓							
Eligibility Criteria	✓	✓						
Medical History, ACR Criteria	✓							
Previous SLE Medications	✓							
Current SLE Medications	✓	✓		✓	✓	✓	✓	✓
Concomitant Medications	✓	✓		✓	✓	✓	✓	✓
Current History / Symptoms / VAS	✓	✓		✓	✓	✓	✓	✓
Physical Examination	✓	✓		✓	✓	✓	✓	✓
ECOG	✓	✓			✓		✓	
Adverse Events		✓	✓	✓	✓	✓	✓	✓
PGA	✓	✓		✓	✓	✓	✓	✓
SLEDAI	✓	✓		✓	✓	✓	✓	✓
Classical BILAG	✓	✓				✓		
Modified BILAG		✓		✓	✓	✓	✓	✓
SF-36®		✓						
SLICC/ACR-DI	✓							
Pregnancy test[1]	✓	✓						
Virological tests[2]	✓							
Safety laboratory tests[3]	✓	✓		✓	✓	✓	✓	✓
SLE Serology I[4]	✓	✓		✓	✓	✓	✓	✓
SLE Serology II[4]	✓	✓				✓		
ECG	✓							
Echocardiogram	✓							
Abdominal Ultrasound	✓							
Lung Function	✓							
Urine analysis[5]	✓	✓				✓		
Kidney biopsy[6]	✓							
Photography[7]		✓				✓		
Cognitive testing[8]	✓							
cMRI[9]	✓							
Cellular Immunology[10]	✓	✓	✓	✓	✓	✓	✓	✓
Urine Cells[11]	✓	✓		✓	✓	✓	✓	✓
Cytokines		✓		✓	✓	✓	✓	✓
Transcriptome		✓		✓				

Procedures	Visit 1	Visit 2	Cycle 1	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
TSDR (Sort)		✓						
TCR Sequencing (Sort)		✓		✓				
Antigen-specific T cells (Sort)	✓							
Treg Function		✓				✓		
Aldesleukin-Abs		✓		✓	✓	✓	✓	✓
Tetanus-Abs		✓						

Continued

	Visit 8 before Cycle 4	Visit 9 after Cycle 4		Visit 10 Follow-up	Visit 11 Termination		Unscheduled Visit
Procedures	day 57 week 9	day 62 week 9		Day 83 (+/- 3d) week 12	Day 125 (+/- 5d) week 18		(any time during study)
Informed Consent							
Demographic Data							
Eligibility Criteria							
Medical History, ACR Criteria							
Previous SLE Medications							
Current SLE Medications	✓	✓		✓	✓		✓
Concomitant Medications	✓	✓		✓	✓		✓
Current History / Symptoms / VAS	✓	✓		✓	✓		✓
Physical Examination	✓	✓		✓	✓		✓
ECOG	✓						
Adverse Events	✓	✓		✓	✓		✓
PGA	✓	✓		✓	✓		✓
SLEDAI	✓	✓		✓	✓		✓
Classical BILAG		✓		✓	✓		
Modified BILAG	✓	✓		✓	✓		✓
SF-36®		✓		✓	✓		
SLICC/ACR-DI		✓			✓		
Pregnancy test[1]		✓			✓		
Virological tests[2]							
Safety laboratory tests[3]	✓	✓		✓	✓		✓
SLE Serology I[4]	✓	✓		✓	✓		✓
SLE Serology II[4]		✓		✓	✓		
ECG				✓			
Echocardiogram				✓			
Abdominal Ultrasound				✓			

Procedures	Visit 8	Visit 9		Visit 10	Visit 11		Unscheduled
Lung Function				✓			
Urine analysis[5]		✓		✓	✓		✓
Kidney biopsy[6]							
Photography[7]		✓		✓	✓		
Cognitive testing[8]				✓			
cMRI[9]				✓			
Cellular Immunology[10]	✓	✓		✓	✓		✓
Urine Cells[11]	✓	✓		✓	✓		
Cytokines	✓	✓		✓	✓		
Transcriptome		✓		✓			
TSDR (Sort)		✓					
TCR Sequen-cing (Sort)		✓		✓			
Antigen-specific T cells (Sort)							
Treg Function		✓					
Aldesleukin-Abs	✓	✓		✓	✓		
Tetanus-Abs		✓		✓			

1. Serological pregnancy test (β-HCG) must be performed for all women of childbearing potential at Visit 1 (screening visit), Visit 2 (baseline visit), at Visit 9 (after the 4th cycle) and at Visit 11 (termination visit).
2. Virological tests include HBsAg, anti-HBs, anti-HBc, anti-HCV and anti-HIV1/2.
3. Safety laboratory tests include hematology, clinical chemistry and protein analyses, coagulation tests, levels of soluble IL-2 receptor (sIL-2R) and analysis of spontaneous urine by dip stick analysis and by determination of protein/creatinine ratio (Section 7.6.4.1).
4. SLE serology I analysis includes the serum concentration of anti-dsDNA-abs, the anti-dsDNA-abs-Titer determined by the Crithidia-IFT and serum levels of circulating immune complexes and of the complement factors C3 and C4 (Section 7.6.4.2).
   SLE serology II analysis includes ANA-Titer, ENA, anti-SmD1-abs, anti-Nucleosome-abs, anti-C1q-abs, Rheumafactor, anti-Cardiolipin-abs, anti-β2-Glycoprotein-abs, anti-Phosphatidylserine-abs, serum-electrophoresis, immunoglobuline isotypes (IgA, IgM, IgG) and β2-Mikroglobulin. The direct and indirect Coombs test will only be performed in patients with history or current laboratory signs of autoimmune hemolytic anemia (Section 7.6.4.2).
5. SLE urine analysis includes microscopic evaluation for active sediment and determination of protein levels in 24h-collected urine and has to be performed only for patients with proven renal involvement. As contamination by menstrual blood will interfere with the results, whether or not the patient is menstruating will be recorded on the CRF.
6. Kidney biopsy for the classification and assessment of the severity of lupus nephritis has to be performed only in patients with signs of active nephritis and if a kidney biopsy, providing sufficient information to relate these histological findings to current kidney abnormalities, has not been performed previously.
7. Photographic documentation of affected skin areas applies only for patients with skin involvement.
8. Cognitive function test by Mini-Mental-State-Test (MMST) applies only for patients with cerebral involvement. Cognitive testing at the follow-up visit will be necessary only for patients with impaired cognitive function assessed at the screening visit.
9. Cerebral magnetic resonance imaging (cMRI) applies only for patients with cerebral involvement. cMRI at screening is necessary unless recent imaging was performed within 6 months prior to the sscreening visit (Visit 1). cMRI imaging at the follow-up visit has to be performed only in case of pathologic findings at the screening visit.
10. Cellular Immunology assessments include phenotypic analyses of different immune cells, SIGLEC-1 expression on monocytes, and analysis of p-STAT-5 (Section 7.6.5). Only during the 1st treatment cycle these analyses will be performed daily (day 1-5) without SIGLEC-1 expression on monocytes.
11. Phenotypic analysis and quantification of immune cells in the urine has to be performed only in patients with proven renal involvement.

2. SUMMARY OF EFFICACY RESULTS

2.1 Primary Endpoint and main Secondary Endpoints

Parameter (unit)	Baseline (day 1, week 1)	Endpoint (day 62, week 9)	p-value: trial population only (n=10)	p-value: total incl. comp. use (n=12)
Primary endpoint				
CD25hi cells in % of CD3+CD4+FoxP3+CD127lo Treg	10·49 (2·08-13·88)	37·25 (28·68-52·63)	**0·0020**	**0·0005**
Secondary endpoints				
Disease activity measures				
SELENA-SLEDAI (score)	10·0 (8·0-13·5)	5·0 (4·0-11·0)	**0·0410**	**0·0103**
SLEDAI Flare Index (SFI)				
Mild or moderate flare (patients)	5 (46·7%)	3 (25·0%)	N/A	N/A
Severe flare (patients)	0 (0%)	0 (0%)	N/A	N/A
BILAG 2004 Index				
BILAG Category A (number of domains)	7	4	N/A	N/A
BILAG Category B (number of domains)	11	3	N/A	N/A
BILAG Category C (number of domains)	9	11	N/A	N/A
BILAG Category D (number of domains)	0	7	N/A	N/A
PGA (x/3)	1·65 (1·50-2·00)	1·00 (0·53-1·88)	**0·0039**	**0·0010**
VAS (x/100)	50·0 (35·0-67·5)	50·0 (32·5-70·0)	0·5391	0·4688
SLICC/ACR-DI (score)	1·0 (0·0-2·75)	1·0 (0·0-2·75)	>0·9999	>0·9999
GCS dose (mg/day)	8·75 (5·63-13·75)	8·75 (5·00-10·00)	0·6250	>0·9999
Serological parameters				
Complement factor C3 (mg/L)	775·0 (595·0-805·0)	805·0 (712·5-877·5)	**0·0078**	**0·0078**
Complement factor C4 (mg/L)	85·0 (62·5-110·0)	95·0 (62·5-117·5)	0·1875	0·2188
Circulating immune complexes (µg/mL)	14·35 (7·68-27·70)	11·45 (7·33-24·83)	0·0840	0·1294
Autoantibodies				
ANA (Titer)	1:1280 (1:640-1:2560)	1:1280 (1:640-1:2560)	0·5000	0·3750
Anti-dsDNA-Abs IgG (U/mL)	78·10 (29·65-191·70)	75·75 (22·65-156·90)	0·5566	0·8501
Anti-Nucleosome-Abs (U/mL)	155·0 (40·4-1963·0)	114·8 (34·1-200·0)	0·9453	0·9453
Anti-SmD1-Abs (U/mL)	34·15 (12·90-79·90)	40·95 (23·40-81·13)	0·5703	0·4648
Anti-C1q-Abs (U/mL)	10·1 (5·2-19·4)	11·1 (4·1-18·7)	0·6719	0·5078
Anti-Cardiolipin-Abs IgM (U/mL)	4·20 (1·15-15·75)	4·80 (1·20-18·20)	0·9375	0·9999
Anti-Cardiolipin-Abs IgG (U/mL)	3·90 (3·10-9·85)	5·10 (2·40-10·90)	0·9375	0·9999

Data are median with IQR, n (%), or n. Treg, regulatory T cell; SELENA-SLEDAI, Safety of Estrogens in Lupus National Assessment Systemic Lupus Erythematosus Disease Activity Index; BILAG, British Isles Lupus Assessment Group; PGA, physician's global assessment; VAS, visual analogue scale; SLICC/ACR-DI, Systemic Lupus International Collaborating Clinics / American College of Rheumatology Damage Index; GCS, glucocorticosteroids; ANA, anti-nuclear antibodies; abs, antibodies. Wilcoxon signed-rank test was used to compare changes between baseline and the endpoint at day 62 (week 9).

2.2. Individual changes in clinical parameters

(includes data from the two subjects (P1 and P1) treated in a compassionate use setting before the start of the trial)

	Baseline (day 1, week 1)					End point (day 62, week 9)				
Patient	**SELENA-SLEDAI (items)**	**SFI (items)**	**PGA**	**BILAG domain / category**	**GCS (mg/day)**	**SELENA-SLEDAI (items)**	**SFI (items)**	**PGA**	**BILAG domain / category**	**GCS (mg/day)**
AA (NR)	14 (CV, Ra, Alo, Co)	MF (DR, Pro, CV)	2·0	MC: A MS: C	20·0	12 (CV, Ra, Alo)	MF (DR)	2·0	MC: A MS: C	30·0
BB (R)	8 (Ra, MU, Co, DNA)	MF (PR, MU)	1·5	MC: A MS: C	10·0	2 (DNA)	-	0·5	MC: C MS: C	10·0
CC (NR)	16 (CV, Ra, Alo, Co, DNA)	-	2·0	MC: A	7·5	14 (CV, Ra, Co, DNA)	MF (DR, CV, iGCS)	1·5	MC: A	25·0
DD (R,D)	8 (Ar, Co, DNA)	-	2·0	MS: B HAE: C	7·5	4* (Co, DNA)	-	1·0*	MS: C* HAE: C*	7·5*
EE (R)	10 (Ar, Alo, Co, DNA)	MF (Ar)	1·5	MC: C MS: B	5·0	4 (Co, DNA)	-	0·5	MC: C MS: C	5·0
FF (R)	12 (Ar, Ra, Alo, Pe, Co)	-	1·5	MC: B MS: B CR: B HAE: C	15·0	6 (Alo, Pe, Co)	-	1·0	MC: C MS: D CR: B HAE: C	10·0
GG (R)	6 (Ra, Co, DNA)	-	1·5	MC: B MS: C HAE: C	7·5	4 (Co, DNA)	-	0·75	MC: D MS: D HAE: C	7·5
HH (R)	10 (Ar, Ra, Co, DNA)	-	1·5	MC: B MS: A	5·0	4 (Co, DNA)	-	0·0	MC: D MS: D	5·0
II (NR)	10 (Ar, Ra, Co, DNA)	-	2·5	MC: A MS: A	10·0	13 (Ar, Ra, MU, Co, DNA, Leu)	MF (Ar, MU)	2·0	MC: A MS: B	5·0
JJ (NR)	6 (Ra, Alo, Co)	-	2·5	MC: A MS: C	5·0	8 (Ra, Alo, Co, DNA)	-	2·0	MC: A MS: C	5·0
P1 (R)	14 (Ar, Myo, Ra, Co, DNA)	MF (Ar)	1·8	MC: B MS: B	30·0	4 (Co, DNA)	-	0·6	MC: D MS: C	10·0
P2 (R)	12 (Ar, Ra, Pe, Co, DNA)	MF (Ar)	1·5	CS: C MC: C MS: B CR: B	10·0	6 (Pe, Co, DNA)	-	1·0	CS: D MC: C MS: D CR: B	10·0

SELENA-SLEDAI, Safety of Estrogens in Lupus National Assessment Systemic Lupus Erythematosus Disease Activity Index; SFI, SELENA-SLEDAI flare index; PGA, physician's global assessment; BILAG, British Isles Lupus Assessment Group 2004 index; GCS, glucocorticosteroids; NR, non-responder; R, responder; SLEDAI items: CV, cutaneous vasculitis; Ar, arthritis; Myo, myositis; Ra, rash; Alo, alopecia; MU, mucosal ulcers; Pe, pericarditis; Co, low complement; DNA, anti-dsDNA-abs; Leu, leukopenia; MF, mild or moderate flare; SFI items: DR, discoid rash; Pro, lupus profundus / panniculitis; CV, cutaneous vasculitis; PR, photosensitive rash; MU, mucosal ulcers; Ar, Arthritis, iGCS, increase in glucocorticosteroids; BILAG domains: MC, mucocutaneous; MS, musculoskleletal; HAE, haematological; CR, cardiorespiratory; CS, constitutional. *last observation carried forward (LOCF).

3. SUMMARY OF SAFETY DATA

3.1 List of Adverse Events (AEs)

Complete study period: 31.03.2014-20.10.2016 (trial population only, n=10)

Onset date of AE	*Patient-ID*	*Age*	*Sex*	*AE description according to CTCAE (v4.03)*	*Severity grade of AE*	*Relationship to IMP*	*Outcome*	*Resolution date of AE*
23.04.2014	01	26	m	Injection site reaction	mild	definitely	resolved	30.04.2014
25.04.2014	01	26	m	Diarrhea	mild	possibly	resolved	13.05.2014
08.05.2014	01	26	m	Fever	moderate	definitely	resolved	12.05.2014
08.05.2014	01	26	m	Flu-like symptoms	moderate	definitely	resolved	12.05.2014
07.05.2014	01	26	m	Injection site reaction	mild	definitely	resolved	18.05.2014
13.05.2014	01	26	m	Myalgia	mild	probably	resolved	18.05.2014
25.05.2014	01	26	m	Paresthesia	mild	possibly	resolved	18.06.2014
22.05.2014	01	26	m	Gum Infection (fungal)	mild	possibly	resolved	18.06.2014
28.05.2014	01	26	m	Injection site reaction	mild	definitely	resolved	05.06.2014
28.05.2014	01	26	m	Diarrhea	mild	definitely	resolved	03.06.2014
28.05.2014	01	26	m	Myalgia	mild	definitely	resolved	04.06.2014
28.05.2014	01	26	m	Productive Cough	mild	unrelated	resolved	18.06.2014
28.05.2014	01	26	m	Headache	mild	definitely	resolved	02.06.2014
18.06.2014	01	26	m	Fever	mild	definitely	resolved	23.06.2014
18.06.2014	01	26	m	Headache	mild	definitely	resolved	23.06.2014
18.06.2014	01	26	m	Nausea	mild	possibly	resolved	23.06.2014
01.07.2014	01	26	m	Fever	moderate	unrelated	resolved	12.07.2014
01.07.2014	01	26	m	Bronchial Infection	severe	unrelated	resolved	17.07.2014
11.07.2014	01	26	m	Gum Infection (fungal)	mild	unrelated	resolved	17.07.2014
24.07.2014	01	26	m	Fever	mild	unrelated	resolved	05.08.2014
24.07.2014	01	26	m	Skin Infection	severe	unrelated	resolved	05.08.2014
24.07.2014	01	26	m	Gum Infection (fungal)	moderate	unrelated	improved	N/A
14.08.2014	01	26	m	Skin Infection	severe	unrelated	resolved	21.08.2014
10.08.2014	02	38	f	Fever	mild	possibly	resolved	10.08.2014
10.08.2014	02	38	f	Headache	mild	possibly	resolved	10.08.2014
10.08.2014	02	38	f	Injection site reaction	mild	definitely	resolved	13.08.2014
22.08.2014	02	38	f	Fever	mild	definitely	resolved	24.08.2014
22.08.2014	02	38	f	Chills	mild	definitely	resolved	24.08.2014
22.08.2014	02	38	f	Myalgia	mild	definitely	resolved	24.08.2014
22.08.2014	02	38	f	Injection site reaction	mild	definitely	resolved	30.08.2014
11.09.2014	02	38	f	Injection site reaction	mild	definitely	resolved	20.09.2014
13.09.2014	02	38	f	Sore throat	mild	possibly	resolved	14.09.2014
03.10.2014	02	38	f	Fever	mild	definitely	resolved	05.10.2014
03.10.2014	02	38	f	Chills	mild	definitely	resolved	05.10.2014
03.10.2014	02	38	f	Myalgia	mild	definitely	resolved	05.10.2014
02.10.2014	02	38	f	Injection site reaction	mild	definitely	resolved	10.10.2014
01.11.2014	02	39	f	Fever	mild	definitely	resolved	01.11.2014
01.11.2014	02	39	f	Chills	mild	definitely	resolved	01.11.2014
08.11.2014	02	39	f	Fever	mild	definitely	resolved	08.11.2014

08.11.2014	02	39	f	Chills	mild	definitely	resolved	08.11.2014
25.11.2014	02	39	f	Productive cough	mild	unrelated	resolved	08.12.2014
25.11.2014	02	39	f	Myalgia	mild	unrelated	resolved	08.12.2014
25.11.2014	02	39	f	Rhinitis infective	mild	unrelated	resolved	08.12.2014
12.11.2014	03	30	f	Injection site reaction	mild	definitely	resolved	17.11.2014
21.11.2014	03	30	f	Nausea	mild	possibly	resolved	01.12.2014
26.11.2014	03	30	f	Injection site reaction	mild	definitely	resolved	03.12.2014
26.11.2014	03	30	f	Fever	mild	probably	resolved	27.11.2014
26.11.2014	03	30	f	Myalgia	mild	probably	resolved	27.11.2014
26.11.2014	03	30	f	Sore throat	mild	possibly	resolved	27.11.2014
26.11.2014	03	30	f	Rhinitis infective	mild	possibly	resolved	27.11.2014
29.11.2014	03	30	f	Irregular menstruation	mild	possibly	resolved	04.12.2014
17.12.2014	03	30	f	Injection site reaction	mild	definitely	resolved	22.12.2014
18.12.2014	03	30	f	Myalgia	mild	probably	resolved	19.12.2014
21.12.2014	03	30	f	Sore throat	mild	possibly	resolved	22.12.2014
08.01.2015	03	30	f	Myalgia	mild	probably	resolved	09.01.2015
30.01.2015	03	30	f	Allergic reaction	moderate	unrelated	resolved	30.01.2015
11.01.2015	04	27	f	Sinus tachycardia	mild	possibly	resolved	12.01.2015
08.01.2015	04	27	f	Injection site reaction	mild	definitely	resolved	20.01.2015
21.01.2015	04	27	f	Injection site reaction	mild	definitely	resolved	30.01.2015
16.02.2015	04	27	f	Peripheral ischemia	moderate	possibly	resolved	23.02.2015
27.02.2015	04	27	f	Peripheral ischemia	severe	possibly	resolved with sequela	03.03.2015
06.03.2015	04	27	f	Fever	mild	unrelated	resolved	06.03.2015
06.03.2015	04	27	f	Headache	moderate	unrelated	resolved	06.03.2015
02.02.2015	05	39	f	Injection site reaction	mild	definitely	resolved	11.02.2015
11.02.2015	05	39	f	Lymphadenopathy	mild	unrelated	resolved	16.02.2015
04.03.2015	05	39	f	Injection site reaction	mild	definitely	resolved	09.03.2015
22.03.2015	05	39	f	Dysarthria	moderate	unrelated	resolved	23.03.2015
22.03.2015	05	39	f	Dizziness	mild	unrelated	resolved	23.03.2015
27.03.2015	05	39	f	Fever	moderate	definitely	resolved	29.03.2015
27.03.2015	05	39	f	Chills	mild	definitely	resolved	29.03.2015
27.03.2015	05	39	f	Myalgia	mild	definitely	resolved	29.03.2015
28.03.2015	05	39	f	Rhinitis infective	mild	possibly	resolved	30.03.2015
28.03.2015	05	39	f	Pleuritic pain	mild	possibly	resolved	29.03.2015
30.03.2015	05	38	f	Sinus tachycardia	mild	possibly	resolved	30.03.2015
01.04.2015	04	28	f	Skin Infection	severe	unrelated	resolved with sequela	09.04.2015
01.04.2015	04	28	f	Peripheral ischemia	severe	unrelated	ongoing	N/A
01.04.2015	04	28	f	Gum Infection (fungal)	mild	unrelated	resolved	09.04.2015
01.04.2015	05	39	f	Allergic reaction	mild	unrelated	resolved	09.04.2015
24.06.2015	06	43	f	Injection site reaction	mild	definitely	resolved	29.06.2015
06.07.2015	06	43	f	Productive cough	mild	unrelated	resolved	N/A
09.07.2015	06	43	f	Injection site reaction	mild	definitely	resolved	15.07.2015
09.07.2015	06	43	f	Edema face	mild	possibly	resolved	12.07.2015

13.07.2015	06	43	f	Injection site reaction	moderate	definitely	ongoing	N/A
30.07.2015	06	43	f	Injection site reaction	mild	definitely	resolved	05.08.2015
30.07.2015	06	43	f	Edema face	mild	possibly	resolved	02.08.2015
31.07.2015	06	43	f	Myalgia	mild	possibly	resolved	03.08.2015
20.08.2015	06	43	f	Edema face	moderate	possibly	resolved	27.08.2015
06.09.2015	06	43	f	Fatigue	mild	unrelated	ongoing	N/A
09.09.2015	06	43	f	Myalgias	mild	unrelated	resolved	05.10.2015
10.10.2015	06	43	f	Myalgias	mild	unrelated	ongoing	N/A
12.07.2015	07	28	f	Nausea	mild	unrelated	resolved	12.07.2015
12.07.2015	07	28	f	Vomiting	mild	unrelated	resolved	12.07.2015
12.07.2015	07	28	f	Diarrhea	mild	unrelated	resolved	12.07.2015
12.07.2015	07	28	f	Headache	mild	unrelated	resolved	12.07.2015
03.08.2015	07	28	f	Injection site reaction	mild	definitely	resolved	05.08.2015
16.08.2015	07	28	f	Injection site reaction	mild	definitely	resolved	17.08.2015
27.08.2015	07	29	f	Urinary tract infection	moderate	unrelated	resolved	02.09.2015
07.09.2015	07	29	f	Urinary tract infection	moderate	unrelated	resolved	12.09.2015
08.09.2015	07	29	f	Hematuria	mild	unrelated	resolved	12.09.2015
21.09.2015	07	29	f	Bronchial Infection	moderate	unrelated	resolved	10.10.2015
30.09.2015	07	29	f	Urinary tract infection	severe	unrelated	resolved	12.10.2015
15.11.2015	07	29	f	Productive cough	mild	unrelated	ongoing	N/A
01.12.2015	07	29	f	Urinary tract infection	moderate	unrelated	ongoing	N/A
01.02.2016	08	53	f	Sore throat	mild	unrelated	resolved	03.02.2016
03.02.2016	08	53	f	Fatigue	mild	possibly	resolved	08.02.2016
04.02.2016	08	53	f	Injection site reaction	mild	definitely	resolved	10.02.2016
04.02.2015	08	53	f	Palpitations	mild	unrelated	resolved	07.02.2016
09.02.2016	08	53	f	Upper respiratory infection	moderate	unrelated	resolved	02.03.2016
17.02.2016	08	53	f	Headache	severe	possibly	resolved	19.02.2016
17.02.2016	08	53	f	Nausea	severe	possibly	resolved	18.02.2016
17.02.2016	08	53	f	Dizziness	moderate	possibly	resolved	18.02.2016
17.02.2016	08	53	f	Fatigue	moderate	probably	resolved	27.02.2016
17.02.2016	08	53	f	Injection site reaction	mild	definitely	resolved	27.02.2016
07.03.2016	08	53	f	Dyspepsia	mild	unrelated	resolved	09.03.2016
09.03.2016	08	53	f	Nausea	mild	possibly	resolved	11.03.2016
09.03.2016	08	53	f	Chills	mild	probably	resolved	15.03.2016
09.03.2016	08	53	f	Stomach pain	mild	unrelated	resolved	16.03.2016
09.03.2016	08	53	f	Injection site reaction	mild	definitely	resolved	16.03.2016
09.03.2016	08	53	f	Fatigue	mild	probably	resolved	14.03.2016
09.03.2016	08	53	f	Arthralgia	mild	probably	resolved	13.03.2016
09.03.2016	08	53	f	Laryngopharyngeal dysesthesia	mild	unrelated	resolved	15.03.2016
04.04.2016	08	53	f	Fever	mild	definitely	resolved	25.04.2016
04.04.2016	08	53	f	Arthralgia	mild	definitely	resolved	25.04.2016
04.04.2016	08	53	f	Stomach pain	mild	unrelated	resolved	25.04.2016
04.04.2016	08	53	f	Headache	mild	possibly	resolved	25.04.2016
04.04.2016	08	53	f	Injection site reaction	mild	definitely	resolved	25.04.2016
06.06.2016	09	39	f	Injection site reaction	mild	definitely	resolved	15.06.2016

06.06.2016	09	39	f	Productive cough	mild	unrelated	resolved	15.06.2016
20.06.2016	09	39	f	Injection site reaction	mild	definitely	resolved	06.07.2016
20.06.2016	09	39	f	Arthralgia	mild	definitely	resolved	06.07.2016
20.06.2016	09	39	f	Myalgia	mild	definitely	resolved	06.07.2016
20.06.2016	09	39	f	Fatigue	mild	definitely	resolved	06.07.2016
11.07.2016	09	39	f	Arthralgia	mild	definitely	resolved	27.07.2016
01.08.2016	09	39	f	Injection site reaction	mild	definitely	resolved	22.08.2016
01.08.2016	09	39	f	Arthralgia	mild	definitely	resolved	22.08.2016
01.08.2016	09	39	f	Myalgia	mild	definitely	resolved	22.08.2016
13.06.2016	10	54	f	Injection site reaction	mild	definitely	resolved	23.06.2016
13.06.2016	10	54	f	Arterial hypertension	mild	possibly	resolved	23.06.2016
23.06.2016	10	54	f	Sinusitis	moderate	unrelated	resolved	28.06.2016
28.06.2016	10	54	f	Injection site reaction	mild	definitely	resolved	14.07.2016
28.06.2016	10	54	f	Fever	mild	definitely	resolved	14.07.2016
28.06.2016	10	54	f	Chills	mild	definitely	resolved	14.07.2016
28.06.2016	10	54	f	Fatigue	mild	possibly	resolved	16.08.2016
14.07.2016	10	54	f	Injection site reaction	moderate	definitely	resolved	19.07.2016
19.07.2016	10	54	f	Injection site reaction	mild	definitely	resolved	11.08.2016
19.07.2016	10	54	f	Fever	mild	definitely	resolved	11.08.2016
11.08.2016	10	54	f	Palpitations	mild	unrelated	resolved	16.08.2016
16.08.2016	10	54	f	Injection site reaction	mild	definitely	resolved	06.09.2016
16.08.2016	10	54	f	Flu-like symptoms	mild	definitely	resolved	06.09.2016
06.09.2016	10	54	f	Nausea	mild	unrelated	resolved	20.10.2016
06.09.2016	10	54	f	Sinusitis	mild	unrelated	resolved	20.10.2016
06.09.2016	10	54	f	Rash acneiform	mild	unrelated	resolved	20.10.2016

3.2 List of Serious Adverse Events (SAEs):

Complete Study Period: 31.03.2014-20.10.2016 (trial population only, n=10)

Onset date of AE	*Patient-ID*	*Age*	*Sex*	*AE description according to CTCAE (v4.03)*	*Severity grade of AE*	*Relation-ship to IMP*	*Type of SAE*	*Out-come*	*Resolu-tion date of AE*
01.07.2014	01	26	m	Bronchial infection	severe	unrelated	hospitali-zation	re-solved	17.07.2014
24.07.2014	01	26	m	Skin infection	severe	unrelated	hospitali-zation	re-solved	05.08.2014
14.08.2014	01	26	m	Skin infection	severe	unrelated	hospitali-zation	re-solved	21.08.2014
27.02.2015	04	27	f	Peripheral ischemia	severe	possibly	hospitali-zation	re-solved with sequela	03.03.2015
01.04.2015	04	28	f	Skin Infection / peripheral ischemia	severe	unrelated	hospitali-zation	re-solved with sequela	09.04.2015

3.3 List of relevant abnormal laboratory findings resulting in a dose reduction of aldesleukin and/or classified as adverse events

Complete Study Period: 31.03.2014-20.10.2016 **(trial population only, n=10)**

Onset date of AE	*Patient-ID*	*Age*	*Sex*	*Abnormal Laboratory Finding*	*Severity grade*	*Relation-ship to IMP*	*Out-come*	*Resolu-tion date*
17.07.2014	01	26	m	Neutrophil count decreased	moderate	unrelated	resolved	24.07.2014
22.12.2014	03	30	f	Leukocyte count decreased	moderate	possibly	resolved	07.01.2015
12.01.2015	04	27	f	Lymphocyte count decreased	severe	unrelated	ongoing	N/A
26.01.2015	04	27	f	Fibrinogen increased >25% of ULN	moderate	definitely	resolved	16.02.2015
02.02.2015	05	39	f	Fibrinogen increased >25% of ULN	moderate	definitely	resolved	11.02.2015
03.08.2015	06	43	f	Eosinophil count increased	mild	probably	resolved	19.08.2015
03.08.2015	07	28	f	Lymphocyte count decreased	severe	unrelated	ongoing	N/A

3.4 Aggregate summary tabulation

Complete study period: 31.03.2014-20.10.2016 **(trial population only, n=10)**

System Organ Class (SOC)			Total	IMP related
Blood and lymphatic system disorders			**0**	**0**
Cardiac disorders			**4**	**0**
Congenital, familial and genetic disorders			**0**	**0**
Ear and labyrinth disorders			**0**	**0**
Endocrine disorders			**0**	**0**
Eye disorders			**0**	**0**
Gastrointestinal disorders			**13**	**1 (7.7%)**
	Nausea:	6		0
	Diarrhea:	3		1 (33.3%)
	Stomach pain:	2		0
	Dyspepsia:	1		0
	Vomiting	1		0
General disorders and administration site conditions			**65**	**54 (83.1%)**
	Injection site reaction:	32		32 (100%)
	Fever:	15		11 (73.3%)
	Chills:	7		7 (100%)
	Fatigue:	6		3 (50%)
	Edema face:	3		0
	Flu-like symptoms:	2		1 (50%)
Hepatobiliary disorders			**0**	**0**
Immune system disorders			**3**	**0**
	Allergic reaction:	2		0
	Lymphadenopathy:	1		0
Infections and infestations			**19**	**0**
	Gum infection (fungal):	4		0
	Urinary tract infection:	4		0
	Skin infection:	3		0
	Rhinitis infective:	3		0
	Bronchial infection:	2		0
	Upper respiratory infection:	1		0
	Sinusitis:	2		0
Injury, poisoning and procedural complications			**0**	**0**
Investigations			**7**	**3 (42.9%)**
	Lymphocyte count decreased:	2		0
	Fibrinogen increased:	2		2 (100%)
	Leukocyte count decreased:	1		0
	Neutrophil count decreased:	1		0
	Eosinophil count increased:	1		1 (100%)

Metabolism and nutrition disorders		**0**	**0**
Musculoskeletal and connective tissue disorders		**19**	**15 (78.9%)**
	Myalgia: 14		10 (71.4%)
	Arthralgia: 5		5 (100%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		**0**	**0**
Nervous system disorders		**11**	**2 (18.2%)**
	Headache: 7		2 (28.06%)
	Other: 4		0
Pregnancy, puerperium and perinatal conditions		**0**	**0**
Psychiatric disorders		**0**	**0**
Renal and urinary disorders		**1**	**0**
Reproductive system and breast disorders		**1**	**0**
Respiratory, thoracic and mediastinal disorders		**11**	**0**
	Productive cough: 5		0
	Sore throat: 4		0
	Other: 2		0
Skin and subcutaneous tissue disorders		**1**	**0**
Social circumstances		**0**	**0**
Surgical and medical procedures		**0**	**0**
Vascular disorders		**4**	**0**
	Peripheral ischemia: 3		0
	Other: 1		0
TOTAL		**159**	**75 (47.2%)**

3.5 Adverse events per dose/cycle and study periods

(includes data from the two subjects who were treated in a compassionate use setting before the start of the trial)

	AEs per single dose/cycle*			AEs per study period			
	0·75 (10^6 IU)	**1·5 (10^6 IU)**	**3·0 (10^6 IU)**	**Treatment period (d1 - d62)**	**Follow-up period (d63 - d120)**	**Screening period (d-30 - d-1)**	**Complete study period (d-30 - d120)**
Total AEs (n)	15	82	34	131	32	4	167
Total TR-AEs (n)	7	51	22	80	2	0	82
TR-AEs (% of total AEs)	46·7%	62·2%	64·7%	61·1%	6·3%	0	49·1%
Treatment cycles (n)	7	31	8	46	N/A	N/A	N/A
Average AEs per cycle (n)	2·1	2·6	4·3	2·8	N/A	N/A	N/A
Average TR-AEs per cycle (n)	1·0	1·6	2·8	1·7	N/A	N/A	N/A
Grade 1 AEs							
AEs (n)	10	74	26	110	19	4	133
AEs (% of total AEs)	66·7%	90·2%	76·5%	84·0%	59·4%	100·0%	79·6%
TR-AEs (n)	6	48	18	72	2	0	74
TR-AEs (% of total AEs)	40·0%	58·5%	52·9%	55·0%	6·3%	0	44·3%
TR-AEs (% of total TR-AEs)	85·7%	94·1%	81·8%	90·0%	100·0%	0	90·2%
Average AEs per cycle (n)	1·4	2·4	3·3	2·4	N/A	N/A	N/A
Average TR-AEs per cycle (n)	0·9	1·5	2·3	1·6	N/A	N/A	N/A
Grade 2 AEs							
AEs (n)	5	5	6	16	7	0	23
AEs (% of total AEs)	33·3%	6·1%	17·6%	12·2%	21·9%	0	13·8%
TR-AEs (n)	1	3	4	8	0	0	8
TR-AEs (% of total AEs)	6·7%	3·7%	11·8%	6·1%	0	0	4·8%
TR-AEs (% of total TR-AEs)	14·3%	5·9%	18·2%	10·0%	0	0	9·8%
Average AEs per cycle (n)	0·7	0·2	0·8	0·3	N/A	N/A	N/A
Average TR-AEs per cycle (n)	0·1	0·1	0·5	0·2	N/A	N/A	N/A
Grade 3 AEs							
AEs (n)	0	3	2	5	6	0	11
AEs (% of total AEs)	0	3·7%	5·9%	3·8%	18·8%	0	6·6%
TR-AEs (n)	0	0	0	0	0	0	0
TR-AEs (% of total AEs)	0	0	0	0	0	0	0
TR-AEs (% of total TR-AEs)	0	0	0	0	0	0	0
Average AEs per cycle	0	0·1	0·3	0·1	N/A	N/A	N/A
Average TR-AEs per cycle (n)	0	0	0	0	N/A	N/A	N/A

These data pertain to all treated patients including the two patients treated with the study regimen in a compassionate use context before the trial (AA-JJ, P1, P2; n=12). The severity grade was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03). *The highest administered single dose in the cycle was decisive for the dose classification of cycle. AE, adverse events; TR-AE, treatment-related AE (definitely and probably); d, day; N/A, not applicable.

3.6 Changes in safety laboratory parameters

(includes data from the two subjects who were treated in a compassionate use setting before the start of the trial)

Parameter (unit)	Baseline (day 1, week 1)	End point (day 62, week 9)	Patients analyzed	p-value
Haematology				
Hemoglobin (g/dL)	12·5 (11·58-13·80)	11·9 (11·18-12·60)	12 (100%)	0·0068
Leukocytes (counts/nL)	7·285 (4·99-9·23)	5·65 (3·83-7·15)	12 (100%)	0·0010
Thrombocytes (counts/nL)	213 (141-255)	194 (154-255)	12 (100%)	0·9248
Neutrophils (counts/nL)	4·80 (3·79-8·19)	4·15 (2·74-5·21)	12 (100%)	0·0425
Lymphocytes (counts/nL)	0·70 (0·40-1·13)	0·77 (0·42-0·99)	12 (100%)	0·6353
Eosinophils (counts/nL)	0·02 (0·00-0·05)	0·19 (0·03-0·28)	12 (100%)	0·0039
Monocytes (counts/nL)	0·23 (0·16-0·29)	0·15 (0·09-0·24)	9 (75%)	0·1641
Clinical chemistry / proteins				
CRP (mg/L)	3·20 (0·63-14·75)	11·55 (4·20-32·93)	12 (100%)	0·0015
Creatinine (mg/dL)	0·72 (0·66-0·81)	0·71 (0·62-0·78)	12 (100%)	0·4419
Bilirubine (mg/dL)	0·24 (0·19-0·43)	0·24 (0·18-0·26)	12 (100%)	0·3706
ALT/GPT (U/L)	21·00 (13·00-26·75)	18·50 (15·00-29·00)	12 (100%)	0·5317
AST/GOT (U/L)	24·50 (20·50-36·50)	20·50 (18·25-27·25)	12 (100%)	0·0527
gGT (U/L)	18·00 (14·00-60·00)	24·50 (15·00-60·75)	12 (100%)	0·5552
Lipase (U/L)	33·00 (20·50-43·50)	22·50 (16·75-31·75)	12 (100%)	0·0005
Ferritin (µg/L)	72·00 (41·75-103·50)	56·00 (34·25-101·90)	12 (100%)	0·6772
Haptoglobin (g/L)	1·39 (0·55-1·88)	1·67 (1·18-2·26)	10 (83·3%)	0·0059
Cholesterol (mg/dL)	196·5 (176·3-225·8)	185·0 (154·0-212·8)	12 (100%)	0·1240
LDH (U/L)	233·0 (189·5-306·0)	236·5 (182·3-244·3)	12 (100%)	0·1099
CK (U/L)	53·50 (46·50-70·25)	42·00 (27·25-56·25)	12 (100%)	0·0146
NT-proBNP (ng/L)	83·50 (77·00-186·30)	169·00 (77·25-257·50)	12 (100%)	0·0884
TSH (mU/L)	0·99 (0·70-1·62)	1·14 (0·68-1·55)	12 (100%)	0·2334
Coagulation				
Quick (%)	100·0 (87·8-102·0)	104·5 (84·8-108·5)	12 (100%)	0·9873
PTT (s)	34·40 (30·25-41·10)	32·85 (29·70-40·48)	12 (100%)	0·1040
Fibrinogen (g/L)	3·65 (3·04-4·19)	4·03 (3·11-4·86)	12 (100%)	0·0542
D-Dimers (mg/L)	0·43 (0·27-0·88)	0·58 (0·27-1·80)	12 (100%)	0·0547
Factor VIII (%)	176·0 (137·5-229·3)	226·0 (187·3-246·5)	12 (100%)	0·0771
Urine analysis				
Protein concentration (mg/L)	67·30 (46·88-156·20)	85·55 (54·05-325·90)	10 (83·3%)	0·2324
Protein/creatinine ratio (mg/g)	154·5 (98·5-220·3)	124·0 (99·3-232·0)	10 (83·3%)	0·8457
Serology				
α1-Globulin (%)	4·70 (3·70-5·28)	5·65 (4·85-6·60)	12 (100%)	0·0005
α2-Globulin (%)	10·15 (7·93-11·05)	10·55 (9·28-11·25)	12 (100%)	0·0254
β-Globulin (%)	10·20 (9·65-11·23)	10·60 (10·30-11·45)	12 (100%)	0·0112
γ-Globulin (%)	15·45 (13·65-22·75)	15·30 (13·70-21·68)	12 (100%)	0·8042
IgG (g/L)	11·03 (9·91-16·91)	10·72 (9·39-15·64)	12 (100%)	0·3916
IgA (g/L)	2·44 (1·99-3·73)	2·69 (2·13-3·68)	12 (100%)	0·8940
IgM (g/L)	0·81 (0·54-1·25)	0·85 (0·45-1·23)	12 (100%)	0·5186
β2-Mikroglobulin (mg/L)	2·7 (2·0-3·3)	2·7 (2·6-4·1)	11 (91·7%)	0·0215
Soluble IL-2R (U/mL)	692 (473-1034)	2005 (1270-2278)	12 (100%)	0·0005
CD4/CD8 ratio	1·43 (0·64-2·05)	1·925 (1·02-2·52)	12 (100%)	0·0005

Data are median with IQR or n (%). CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; gGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; CK, creatine kinase; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; TSH, thyreoidea-stimulating hormone; PTT, partial thromboplastin time; Ig, immunoglobulin; ANA, anti-nuclear antibodies; abs, antibodies. Wilcoxon signed-rank test was used to compare changes between day 1 (baseline) and day 62 (end point).

3.7 Diagnostic safety procedures

(includes data from the two subjects who were treated in a compassionate use setting before the start of the trial)

Procedure / findings	Before treatment (screening period)	After treatment (follow-up period)	Patients analysed	p-value
12-lead ECG			12 (100%)	
Normal result	11 (91·7%)	10 (83·3%)		N/A
Supraventricular extrasystole	1 (8·3%)	2 (16·6%)		N/A
Sinus tachycardia	0 (0%)	1 (8·3%)		N/A
Abdominal ultrasound			10 (83·3%)	
Normal result	4 (40%)	3 (30%)		N/A
Steatosis hepatis	4 (40%)	4 (40%)		N/A
Angiolipoma of kidney	1 (10%)	1 (10%)		N/A
Hemangioma of liver	1 (10%)	1 (10%)		N/A
Cholecystolithiasis	1 (10%)	1 (10%)		N/A
State after splenectomy	2 (20%)	2 (20%)		N/A
Lipomatosis of pancreas	0 (0%)	1 (10%)		N/A
Echocardiography			11 (91·7%)	
Normal result	8 (72·7%)	8 (72·7%)		N/A
Left ventricular hypertrophy	1 (9·1%)	1 (9·1%)		N/A
Pericard effusion	2 (18·2%)	2 (18·2%)		N/A
Lung function tests			10 (83·3%)	
FVC (% of predicted)	104·0 (95·6-118·1)	102·3 (94·3-113·0)		0·2246
FEV1 (% of predicted)	96·5 (85·7-104·9)	95·2 (83·0-100·6)		0·2637
DLCO-SB (% of predicted)	66·0 (57·5-75·7)	56·6 (49·9-76·5)		0·1602
KCO (% of predicted)	70·1 (60·0-91·7)	68·6 (53·5-86·9)		0·4316

ECG, electrocardiogram; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; DLCO-SB, single-breath diffusing capacity of the lung for carbon monoxide; KCO, carbon monoxide transfer coefficient. Wilcoxon signed-rank test was used to compare changes between the screening and the follow-up period.

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