Clinical trial results:
Alemtuzumab in Autoimmune Inflammatory Neurodegeneration: Mechanisms of Action and Neuroprotective Potential

Summary

EudraCT number	2014-000709-10
Trial protocol	DE
Global end of trial date	02 November 2020

Results information

Result version number	v1 (current)
This version publication date	18 November 2021
First version publication date	18 November 2021

Trial information

Trial identification

Sponsor protocol code	UKM12_0026

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02419378
WHO universal trial number (UTN)	U1111-1156-6489

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Münster
Sponsor organisation address	Albert-Schweitzer-Campus 1, Münster, Germany, 48149
Public contact	Klinik für Allgemeine Neurologie, Universitätsklinikum Münster, +49 2518344443, tobias.ruck@ukmuenster.de
Scientific contact	Klinik für Allgemeine Neurologie, Universitätsklinikum Münster, +49 2518344443, tobias.ruck@ukmuenster.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	07 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2020
Global end of trial reached?	Yes
Global end of trial date	02 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Combining clinical data with ex vivo and in vitro data, the study aims to shed more light on the mechanisms of action and the neuroprotective potential of alemtuzumab

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines in Good Clinical Practice. The study was not started before the competent ethics committee had given a favorable opinion. Written informed consent was obtained from all patients and the study was only conducted as approved by the Ethics committee and the competent authority. Amendments were only implemented after approval.

Background therapy:

On Days 1, 2, and 3 of alemtuzumab treatment at months 0 and 12, patients received corticosteroid premedication to prevent infusion associated reactions (IAR). All patients also received oral prophylaxis for herpes infection starting on the first day of each alemtuzumab cycle and continuing for a minimum of 1 month after the last day of each cycle.

Evidence for comparator:

No comparator was used in this study.

Actual start date of recruitment	06 May 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

RRMS (relapsing remitting multiple sclerosis) patients were recruited at the Münster University Hospital (UKM) in Germany. The recruitment period was from May 2015 to June 2017.

Pre-assignment

Screening details:

The study included patients diagnosed with highly active RRMS and indicated to receive treatment with alemtuzumab.

Pre-assignment period milestones

Number of subjects started	19
Number of subjects completed	15

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening Failure: 4

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	Alemtuzumab

Arm description:

Each RRMS patient was treated with alemtuzumab at month 0 and month 12. Patients were followed for three years within the study after their first treatment (month 0) with efficacy and safety assessments on at least semiannual visits. Beyond, there were monthly blood and urine samplings to monitor for autoimmune diseases which may be carried out by a local physician. Patients were strongly advised to continue monitoring for autoimmune diseases beyond study participation, until 48 months after last administration of alemtuzumab.

Arm type	Experimental
Investigational medicinal product name	Lemtrada
Investigational medicinal product code	
Other name	Alemtuzumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Alemtuzumab (Lemtrada) was administered by daily intravenous infusions in a supervised medical setting. Dosage was 12 mg/day for 5 consecutive days at month 0 (60 mg total dose) and for 3 consecutive days at month 12 (36 mg total dose).

Number of subjects in period 1[1]	Alemtuzumab
Started	15
Completed	12
Not completed	3
Non-medical event	1
Lack of efficacy	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 19 RRMS patients were enrolled in the study and assessed for eligibility. Because 4 patients did not meet the inclusion criteria, only 15 RRMS patients entered the baseline period.

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	15	15	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	9	9	
Male	6	6	

End points

End points reporting groups

Reporting group title	Alemtuzumab

Reporting group description:

Each RRMS patient was treated with alemtuzumab at month 0 and month 12. Patients were followed for three years within the study after their first treatment (month 0) with efficacy and safety assessments on at least semiannual visits. Beyond, there were monthly blood and urine samplings to monitor for autoimmune diseases which may be carried out by a local physician. Patients were strongly advised to continue monitoring for autoimmune diseases beyond study participation, until 48 months after last administration of alemtuzumab.

Primary: Efficacy results

End point title	Efficacy results[1]

End point description:

The clinical efficacy results of the study can be found in publication Pfeuffer S, Ruck T et al. 2021. The immunological efficacy results will be published in an additional publication, which is under revision at the time of finalizing this report.

End point type	Primary

End point timeframe:

Baseline (0 month) and 12, 24 and 36 months after initiaton of investigational treatment. In addition, on an optional basis: 6, 18 and 30 months after treatment initiation.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis can be found in publication Pfeuffer S, Ruck T et al. 2021.

End point values	Alemtuzumab			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: cells	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events: For each study patient, beginning with the signing of the informed consent until the end of the study.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Safety group
Reporting group description: Study patients who received at least one dose of alemtuzumab.	

Serious adverse events	Safety group		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 15 (46.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis relapse			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Immune thrombocytopenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Surgical and medical procedures			
Wisdom teeth removal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Chest pain			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Condition aggravated			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	6		
Ill-defined disorder			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Peripheral swelling			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Sensation of foreign body			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Psychiatric disorders			

Depression			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Investigations			
Anti-thyroid antibody positive			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood iron decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vaccination complication			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
Cardiovascular insufficiency			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sinus bradycardia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Nervous system disorders			
Dysaesthesia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	10 / 15 (66.67%)		
occurrences (all)	27		
Hemiparaesthesia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Migraine			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Multiple sclerosis relapse			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	7		
Myoclonus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Speech disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vision blurred			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastric disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Mouth ulceration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		

Oesophageal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	9		
Skin discolouration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Bladder disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Hyperthyroidism			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Arthritis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Limb discomfort			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Muscle tightness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Muscle twitching			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Neck pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Fungal infection			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	5		
Gastroenteritis viral			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Gingivitis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Herpes virus infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	6		
Nasal herpes			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	14 / 15 (93.33%)		
occurrences (all)	43		
Oral herpes			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	13		
Pneumonia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sinusitis			

subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	9		
Urinary tract infection			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	6		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lactose intolerance			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2015	Inclusion criteria of the protocol have been amended. • EDSS limit was changed from 0.0 to 4.0 to 0.0 to 5.0. • Patients with a "severe relapse with high disease activity (≥9 T2 hyperintense lesions and ≥1 gadolinium enhancing lesion" may also be included. In addition, the following has been modified in the protocol: • Baseline assessments: An MRI taken within 3 months prior to initiation of therapy with Lemtrada® can be defined as a baseline MRI.
06 June 2016	Exclusion criterion of the protocol has been amended. • Only the differential blood count of the patients must have normalized at the time of screening (not that of the cellular immune status). In addition, the following has been modified in the protocol: • The recruitment period was extended by 12 months.
13 January 2017	• The side effect bradycardia is listed as "Infusion-associated Reaction". • There may be an occurrence of listeriosis/ listeria meningitis with administration of Lemtrada, most commonly within one month of Lemtrada infusion. Therefore, as a precautionary measure patients receiving Lemtrada should avoid intake of raw or undercooked meat, soft cheeses and unpasteurized dairy products until at least one month after Lemtrada treatment.
08 June 2018	• New clinical findings related to idiopathic thrombocytopenic purpura (ITP), nephropathies, thyroid disorders thyroid disorders, infusion-associated reactions (IAR), and severe varicella-zoster virus infections were considered in the protocol. • As a precaution for listeriosis/ listeria meningitis, patients receiving Lemtrada should avoid the intake of raw or undercooked meat, soft cheeses, and unpasteurized dairy and unpasteurized dairy products from two weeks before weeks before starting, during, and until at least one month after Lemtrada treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26966029

http://www.ncbi.nlm.nih.gov/pubmed/33712515