Clinical trial results:
Treatment of newly diagnosed moderate or severe chronic graft-versus-host disease with prednisone and everolimus (PredEver first)
- A prospective multicenterphase IIA study -

Summary

EudraCT number	2011-004847-35
Trial protocol	DE
Global end of trial date	07 February 2018

Results information

Result version number	v1 (current)
This version publication date	22 January 2022
First version publication date	22 January 2022
Summary attachment (see zip file)	Clinical study report Synopsis (PredEver First_CSR-Synopsis_V01.00_20190331.pdf)

Trial information

Trial identification

Sponsor protocol code	PredEver_first

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Hamburg Eppendorf
Sponsor organisation address	Martinistrasse 52, Hamburg, Germany, 20246
Public contact	Coordinating Investigator, University Medical Center Hamburg-Eppendorf, 0049 407410 55250, ayuketang@uke.de
Scientific contact	Coordinating Investigator, University Medical Center Hamburg-Eppendorf, 0049 407410 55250, ayuketang@uke.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	31 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 February 2018
Global end of trial reached?	Yes
Global end of trial date	07 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to investigate the clinical benefit of treatment with prednisone and everolimus in patients with chronic GVHD.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, the general principles indicated in the Declaration of Helsinki, and all applicable regulatory requirements. Prior to study initiation the study protocol was reviewed and approved by an Independent Ethics Committee (IEC). The study, all study procedures and the risks and benefits were explained to the subjects by responsible investigators and written informed consent were collected prior to any study related examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	28
From 65 to 84 years	8

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at nine sites in Germany. The sites were loated at (university) hospital's departments of stem cell transplantation, internal medicine or hematology. Patient recruitment was performed on sites by trained investigators who provided written and verbal information before obtaining written informed consent.

Pre-assignment

Screening details:

Written informed consent before any study specific medical procedures, inclusion/exclusion citeria check, laboratory screening assessments, medical history and prior/concomitant medication recording, comprehensive assessment of organ involvement i.e. CGvHD disease status according to NIH criteria. Screening period = 14 days

Pre-assignment period milestones

Number of subjects started	38[1]
Number of subjects completed	36

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failures: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 38 patients were consented and started the study screening, 2 patients were screening failures and did not enter the treatment period. 36 patients were enrolled for treatment.

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	first line Prednisolon + Everolimus Treatment (PredEver first)

Arm description:

In this single-arm study patients were allocated to combination therapy with prednisone and everolimus. After diagnosis of cGvHD patients received prednisone 1 mg/kg BW once daily in the morning (orally or I.V.) and everolimus 0.75 mg twice daily orally (targeted trough level 3-8 µg/l). In patients with abnormal liver function test results, the initial dose of everolimus was 0.25 mg twice daily. Depending on the patients's response (CR or PR) prednisone dose tapering was performed. Dose adjustments of everolimus were performed according to clinical judgement of the local physician. Patients were treated on the protocol for a maximum of 12 months.

Arm type	Experimental
Investigational medicinal product name	Prednisone (merchandise)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

5 mg / 20 mg / 50 mg (merchandise), orally or intravenous, initial prednisone dose was 1 mg/kg body weight once daily in the morning for at least two weeks.
stepwise tapering upon CR: duration of each step 2 weeks (1.0 mg to 0.3 mg) or 4 weeks (0.2 mg - 0 mg), Steps: 1.0 mg, 0.8 mg, 0.6 mg, 0.4 mg, 0.3 mg, 0.2 mg, 0.1 mg, 0.05 mg, 0.05 mg (every other day), 0.025 mg (every other day), 0 mg.
In case of flare, tapering may be halted or prednisone increased two to three steps back.
Stepwise tapering upon PR: Duration of each step 2 weeks (1.0 mg to 0.6 mg), 3 weeks (0.5 mg to 0.4

mg) or 4 weeks (0.3 mg – 0.05 mg [every other day])
Steps: 1.0 mg, 0.8 mg, 0.6 mg, 0.4 mg, 0.3 mg, 0.2 mg, 0.1 mg, 0.05 mg, 0.05 mg (every other day).
In case of flare, tapering may be halted or prednisone increased two to three steps back.

Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	Certican
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.25 mg / 0.50 mg / 0.75 mg / 1.00 mg (provided by Novartis Pharma GmbH)
Whole tablets or dispersible tablets were admimistered, initial dose was 0,75 mg twice daily. The dose should have been adjusted to a
targeted trough serum level of 3-8 µg/l, measured by HPLC or immunoassay four to five days after the previous dose change. Dose adjustment was according to clinical judgement of the local physician depending on co-medication, toxicity and serum levels.
In patients with abnormal liver function test results, the initial dose of everolimus was 0.25 mg twice daily. Close monitoring of serum levels at start of treatment and after any dose change was performed for 2 weeks (twice weekly). Increment of daily dose should not have surpassed 0.5 mg within one week.

Number of subjects in period 1	first line Prednisolon + Everolimus Treatment (PredEver first)
Started	36
Completed	19
Not completed	17
Adverse event, serious fatal	2
Screening failures (retrospective)	2
Adverse event, non-fatal	4
Lack of efficacy	8
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	36	36	
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)	28	28	
From 65-84 years	8	8	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	52.4		
standard deviation	± 14.3	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	23	23	

End points

End points reporting groups

Reporting group title	first line Prednisolon + Everolimus Treatment (PredEver first)

Reporting group description:

In this single-arm study patients were allocated to combination therapy with prednisone and everolimus. After diagnosis of cGvHD patients received prednisone 1 mg/kg BW once daily in the morning (orally or I.V.) and everolimus 0.75 mg twice daily orally (targeted trough level 3-8 µg/l). In patients with abnormal liver function test results, the initial dose of everolimus was 0.25 mg twice daily. Depending on the patients's response (CR or PR) prednisone dose tapering was performed. Dose adjustments of everolimus were performed according to clinical judgement of the local physician. Patients were treated on the protocol for a maximum of 12 months.

Primary: Proportion of patients with treatment success at 6 months

End point title	Proportion of patients with treatment success at 6 months[1]

End point description:

Treatment success was defined as: Patient being alive and having achieved a CR or PR of cGvHD without addition of secondary systemic treatment for cGvHD and without development of relapse of underlying disease after 6 months from treatment first intake. Addition of any immunosuppressive or immunomodulatory systemic therapy aimed at treating or controlling symptoms of cGvHD is considered treatment failure.

End point type	Primary

End point timeframe:

start of treatment till week 24 (6 months)

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: descriptive analysis for rate of treatment success at 6 months was performed for primary endpoint

End point values	first line Prednisolon + Everolimus Treatment (PredEver first)			
Subject group type	Reporting group			
Number of subjects analysed	34[2]			
Units: percent				
number (confidence interval 95%)	55.9 (39 to 71)			

Notes:

[2] - final analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival rate

End point title	Overall survival rate

End point description:

Proportion of patients experiencing death

End point type	Secondary

End point timeframe:

from time of enrollment until end of follow-up.

End point values	first line Prednisolon + Everolimus Treatment (PredEver first)			
Subject group type	Reporting group			
Number of subjects analysed	34[3]			
Units: percent				
number (confidence interval 95%)	20.5 (10 to 37)			

Notes:

[3] - final analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (speed of first response)

End point title	Time to response (speed of first response)

End point description:

Speed of first response was defined as the weeks between the date of first study medication intake and the date of visit at which the first response (either CR or PR) occurred. Subjects without a response or who are discontinued before having it were considered as "censored" at the date of end of study.

End point type	Secondary

End point timeframe:

Start of treatment until date of visit at which the first response occurred (evaluation until month 12 visit)

End point values	first line Prednisolon + Everolimus Treatment (PredEver first)			
Subject group type	Reporting group			
Number of subjects analysed	34[4]			
Units: weeks				
median (confidence interval 95%)	2.3 (2.1 to 2.6)			

Notes:

[4] - final analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure

End point title	Time to treatment failure

End point description:

Treatment failure being defined as progression of cGvHD after ≥ 2 weeks in any organ, lack of response (CR/PR) after 12 weeks and/or addition of secondary systemic treatment for cGvHD. Subjects without an event or who are discontinued before having it were considered as "censored" at the date of end of study.

The revised analysis set only body systems eye, genitalia, gastrointestinal tract, joints, liver, mouth and skin were considered for the evaluation of 'progression of cGvHD after or at two weeks in any organ'. Eosinophilia, oesophageal involvement and myositis were not considered.

End point type	Secondary

End point timeframe:

start of treatment until two weeks (progression of cGvHD) and/or until twelve weeks (lack of response) and/or untill addition of secondary systemic treatment for cGVHD

End point values	first line Prednisolon + Everolimus Treatment (PredEver first)			
Subject group type	Reporting group			
Number of subjects analysed	34[5]			
Units: weeks				
median (inter-quartile range (Q1-Q3))	24.7 (18.1 to 53.1)			

Notes:

[5] - final analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients experiencing relapses

End point title	Proportion of patients experiencing relapses

End point description:

This endpoint was the evaluation of the relapse rate of underlying malignancies of patients treated with prednisone and everolimus for cGvHD and was evaluated in the form of proportion of patients with relapses from enrollment until end of follow up.
Patients discontinuing treatment prematurely or discontinuing treatment phase for reasons other than a recurrence of malignancies were censored at the date of study discontinuation.

End point type	Secondary

End point timeframe:

from start of treatment (enrollment) until end of follow up phase (1 year treatment + 1 year Follow-up)

End point values	first line Prednisolon + Everolimus Treatment (PredEver first)			
Subject group type	Reporting group			
Number of subjects analysed	34[6]			
Units: percent				

number (confidence interval 95%)	5.9 (2 to 19)			

Notes:

[6] - final analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients showing pre-defined side effects

End point title	Proportion of patients showing pre-defined side effects

End point description:

This endpoint was the assessment of adverse events including the side effects of prednisone and everolimus in patients with cGvHD, with particular attention to the incident rates of thrombotic microangiopathy (TMA), non-infectious pneumonitis (NIP) and avascular osteonecrosis.

End point type	Secondary

End point timeframe:

start of treatment until end of treatment

End point values	first line Prednisolon + Everolimus Treatment (PredEver first)			
Subject group type	Reporting group			
Number of subjects analysed	34[7]			
Units: number of patients	0			

Notes:

[7] - final analysis

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from the time point of signed inform consent.

Adverse event reporting additional description:

Primary analysis of safety was performed with the safety population, which included 36 patients. As 2 patients deemed screening failures retrospectively, received the study drug, it was decided to include also these patients in the safety analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	first line Prednisolon + Everolimus Treatment (PredEver first)

Reporting group description: -

Serious adverse events	first line Prednisolon + Everolimus Treatment (PredEver first)		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 36 (52.78%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	4		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoproliferative disorder			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Plasma cell myeloma recurrent			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polyserositis			

subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Social circumstances				
Pregnancy of partner				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Painful respiration				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumatosis				

subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Depression				
subjects affected / exposed	2 / 36 (5.56%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femoral neck fracture				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure				
subjects affected / exposed	1 / 36 (2.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				

subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Nausea			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Liver disorder			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver injury			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			

subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchopneumopathy			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	first line Prednisolon + Everolimus Treatment (PredEver first)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 36 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Multiple myeloma subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	7 / 36 (19.44%) 10		
Surgical and medical procedures Tooth extraction subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 3		
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) Prexia subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Oedema subjects affected / exposed occurrences (all)	11 / 36 (30.56%) 13 5 / 36 (13.89%) 8 4 / 36 (11.11%) 4 2 / 36 (5.56%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	7 / 36 (19.44%) 8 6 / 36 (16.67%) 6 2 / 36 (5.56%) 2		
Psychiatric disorders			

Insomnia			
subjects affected / exposed	7 / 36 (19.44%)		
occurrences (all)	7		
Depression			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	8		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	12 / 36 (33.33%)		
occurrences (all)	25		
Gamma-glutamyltransferase increased			
subjects affected / exposed	11 / 36 (30.56%)		
occurrences (all)	22		
Blood cholesterol increased			
subjects affected / exposed	9 / 36 (25.00%)		
occurrences (all)	15		
Platelet count decreased			
subjects affected / exposed	7 / 36 (19.44%)		
occurrences (all)	23		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	7		
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	7		
Low density lipoprotein increased			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	7		
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Blood creatine increased			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	5		
High density lipoprotein increased			

subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Immunoglobulins decreased subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 3		
White blood cell count decreased subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4		
Dizziness subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Sciatica subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Syncope subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 5		
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 3		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		
Eye disorders			

Dry eye subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	14 / 36 (38.89%) 22		
Vomiting subjects affected / exposed occurrences (all)	7 / 36 (19.44%) 9		
Nausea subjects affected / exposed occurrences (all)	6 / 36 (16.67%) 8		
Abdominal pain subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 4		
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Aphthous stomatitis subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 6		
Back pain subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 4		
Pain in extremity subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		

Bone pain			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Muscular weakness			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	6		
Sjogren's syndrome			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 36 (30.56%)		
occurrences (all)	14		
Bronchitis			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	6		
Cytomegalovirus infection			
subjects affected / exposed	5 / 36 (13.89%)		
occurrences (all)	6		
BK virus infection			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Oral herpes			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Pneumonia			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	4		
Herpes simplex			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Respiratory syncytial virus infection			

subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Cystitis			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Ear infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Folliculitis			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Gastrointestinal infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Oral candidiasis			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Parainfluenzae virus infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Respiratory tract infection			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	7		
Rhinitis			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	3		
Sinusitis			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	17 / 36 (47.22%)		
occurrences (all)	41		
Hyperglycaemia			
subjects affected / exposed	10 / 36 (27.78%)		
occurrences (all)	24		

Hypercholesterolaemia subjects affected / exposed occurrences (all)	9 / 36 (25.00%) 11		
Hypokalaemia subjects affected / exposed occurrences (all)	8 / 36 (22.22%) 8		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	6 / 36 (16.67%) 9		
Vitamin D deficiency subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		
Decreased appetite subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Diabetes mellitus subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Hyperuricaemia subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Hypocalcaemia subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2013	Subject of the first amendment was to simplify clinical trial routines as well as to correct minor inconsistencies in the protocol. A Data Safety Monitoring Board (DSMB) was created to ensure the safety of the participants, details concerning dose modification and concomitant medication were added, visit schedule was amended by safety visits for additional physical examination, clinical lab tests and concomitant medication. Adaption of assessment of skin manifestation of cGvHD biopsy which was allowed to be organized as per local routine (a central review could still be arranged by each site), and adaption of adverse event documentation.
30 January 2014	Subject of the second amendment was to simplify clinical trial routines as well as to correct minor inconsistencies in the protocol. The number of centers was increased, the duration of the study was prolonged by one year, exclusion criteria 11 was clarified and CNI tapering was prolonged from 1 - 3 to 1 - 4 weeks.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported