Clinical trial results:
A Phase I-IIa trial on low-dose IL-2 (Aldesleukin) treatment for immunological dysregulation in common variable immunodeficiency (CVID)

Summary

EudraCT number	2015-003369-27
Trial protocol	DE
Global end of trial date	05 June 2018

Results information

Result version number	v1 (current)
This version publication date	04 November 2020
First version publication date	04 November 2020

Trial information

Trial identification

Sponsor protocol code	REGAIN

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00010424

Notes:

Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Breisacher Str. 153, Freiburg, Germany, 79110
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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	06 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2018
Global end of trial reached?	Yes
Global end of trial date	05 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety (esp. with respect to autoimmunity) of different doses of low-dose s.c. Aldesleukin treatment in in common variable immunodeficiency (CVID) patients with autoimmune enteropathy (AIE)

Protection of trial subjects:

Risk-based monitoring done according to ICH-GCP E6 and standard operating procedures (SOP) to verify that patients' rights and wellbeing are protected.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	2
EEA total number of subjects	2

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)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	2
Number of subjects completed	2

Period 1

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

Blinding implementation details:

Single arm trial, no blinding possible

Arms

Arm title	Aldesleukin

Arm description:

Patients with autoimmune enteropathy occurring in the context of common variable immunodeficiency were treated with a cyclic, subcutaneous application of IL-2 (Aldesleukin) at different dose levels (0.5-2.0 MIO IE/day) during a period of 4 - 6 months. Each patient started with an induction cycle (1 MIO IE Aldesleukin/day on five consecutive days followed by nine days without treatment). The following maintenance cycles had a duration of three days followed by 11 days without treatment. IL-2 dosage was adjusted according to adverse events, frequency of Treg cells and clinical efficacy.

Arm type	Experimental
Investigational medicinal product name	Aldesleukin
Investigational medicinal product code	
Other name	Interleukin-2, IL-2, Proleukin
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Different dose levels (0.5-2.0 MIO IE/day) during a period of 4 - 6 months. Each patient started with an induction cycle (1 MIO IE Aldesleukin/day on five consecutive days followed by nine days without treatment). The following maintenance cycles had a duration of three days followed by 11 days without treatment. IL-2 dosage was adjusted according to adverse events, frequency of Treg cells and clinical efficacy. Treatment duration was intended to be six months /per patient.

Number of subjects in period 1	Aldesleukin
Started	2
Completed	2

Baseline characteristics

Reporting groups

Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	2	2	
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)	2	2	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	47		
full range (min-max)	36 to 58	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	1	1	

End points

End points reporting groups

Reporting group title	Aldesleukin

Reporting group description:

Patients with autoimmune enteropathy occurring in the context of common variable immunodeficiency were treated with a cyclic, subcutaneous application of IL-2 (Aldesleukin) at different dose levels (0.5-2.0 MIO IE/day) during a period of 4 - 6 months. Each patient started with an induction cycle (1 MIO IE Aldesleukin/day on five consecutive days followed by nine days without treatment). The following maintenance cycles had a duration of three days followed by 11 days without treatment. IL-2 dosage was adjusted according to adverse events, frequency of Treg cells and clinical efficacy.

Primary: Safety (combined primary endpoint)

End point title	Safety (combined primary endpoint)[1]

End point description:

Safety (combined primary endpoint):
- Any adverse event with CTCAE grade ≥ 3 if not defined otherwise below (except injection site reaction grade 3)
- Increasing lymphocytic infiltration or villous atrophy on histopathological analysis/ gastroduodenoscopy
- Flare of pre-existing, previously silent, immune dysregulatory disorder (e.g. lymphocytic lung infiltration) requiring immunosuppressive treatment with > 20mg prednisolone equivalent
- Percentage of Foxp3+CD127lo Treg among CD3+CD4+ T cells > 50%
- Severe impairment of heart, liver or kidney function (CTCAE grade ≥ 3)
- Cytopenia: - leukocyte count: < 2.000/ µl or - neutropenia < 1000/ µl or - platelets: < 50.000/ µl or - haemoglobin <8g/dl
- Development of autoantibodies (ANA, RF) during the treatment phase

End point type	Primary

End point timeframe:

during the trial

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: Only two participants were included in trial. Descriptive statistics were used to evaluate the results of the study.

End point values	Aldesleukin			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Number of adverse events	0			

Statistical analyses

No statistical analyses for this end point

Secondary: IBDQ score

End point title	IBDQ score

End point description:

Increase of IBDQ score by at least 16 points compared to baseline according to the different dose levels.

End point type	Secondary

End point timeframe:
during the trial

End point values	Aldesleukin			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Number of patients	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Stool frequency

End point title	Stool frequency

End point description:
Reduction of daily stool frequency by 3 stools compared to baseline according to the different dose levels

End point type	Secondary

End point timeframe:
during the trial

End point values	Aldesleukin			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Number of patients	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Weight gain

End point title	Weight gain

End point description:
Weight gain of ≥ 2kg at EOT visit compared to baseline in each patient.

End point type	Secondary

End point timeframe:
end of trial

End point values	Aldesleukin			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Number of patients	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Norovirus infection

End point title	Norovirus infection

End point description:

Clearance of (chronic) norovirus infection during treatment was analysed at 2, 4 and 6 months after initiation of treatment in each norovirus-positive patient at baseline. Patient 001 was negative for norovirus infection and therefore not included in this analysis (reporting group). Patient 002 was a norovirus carrier at baseline level and at all control measurements throughout the treatment.

End point type	Secondary

End point timeframe:

2, 4 and 6 months after initiation of treatment

End point values	Aldesleukin			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Number of patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of lymphocytic infiltration and villous atrophy

End point title	Resolution of lymphocytic infiltration and villous atrophy

End point description:

Resolution of lymphocytic infiltration and villous atrophy in gastroduodenoscopy + histopathology will be analyzed in each patient at follow-up compared to baseline.

End point type	Secondary

End point timeframe:

after the low-dose IL-2 treatment

End point values	Aldesleukin			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Number of patients	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion of Tregs

End point title	Expansion of Tregs

End point description:

End point type	Secondary

End point timeframe:

% of Tregs measured before each cycle and on day 4 of every cycle and on day 6 of the induction cycle(s).

End point values	Aldesleukin			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: % of CD25hi Treg	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the treatment and follow-up	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Investigations			
Eosinophil count increased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	3		
Lymphopenia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
General disorders and administration site conditions			

Application site erythema subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Influenza like illness subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 3		
Injection site induration subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Injection site reaction subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 2		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 2		
Rash papular subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Infections and infestations Corona virus infection subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Despite intensive efforts no further eligible patients could be recruited

Notes: