Clinical trial results:
Characterization of human peripheral and intestinal T-cell responses after mucosal antigen exposure: induction of tolerance vs. immunization by oral administration of KLH

Summary

EudraCT number	2011-001232-27
Trial protocol	DE
Global end of trial date	30 June 2015

Results information

Result version number	v1 (current)
This version publication date	28 February 2020
First version publication date	28 February 2020

Trial information

Trial identification

Sponsor protocol code	KLEX

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Dr. Reiner Ullrich, CBF, Medizinische Klinik für Gastroenterologie, Infektiologie und Rheumatologie, reiner.ullrich@charite.de
Scientific contact	Dr. Reiner Ullrich, CBF, Medizinische Klinik für Gastroenterologie, Infektiologie und Rheumatologie, reiner.ullrich@charite.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 June 2014
Global end of trial reached?	Yes
Global end of trial date	30 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safety of immunization with KLH following oral and / or parenteral administration

Protection of trial subjects:

Treated at tertiary care center

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2012
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: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	22
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period: June 26, 2012 to June 4, 2014

Pre-assignment

Screening details:

healthy volunteers including normal blood count, CRP, ALT, GGT, creatinin

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	oral-parenteral (A1)

Arm description:

The subjects of the oral group A1 receive daily 50 mg KLH orally for ten days, followed by two parenteral immunizations with 0.1 mg KLH subcutaneously The subjects of the control group K1 receive only the parenteral immunizations. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Arm type	Experimental
Investigational medicinal product name	Keyhole limpet hemocyanin (KLH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/skin-prick test, Oral solution
Routes of administration	Cutaneous use, Oral use

Dosage and administration details:

The subjects of the oral group A1 receive daily 50 mg KLH orally for ten days, followed by two parenteral immunizations with 0.1 mg KLH subcutaneously The subjects of the control group K1 receive only the parenteral immunizations. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Arm title	control K1

Arm description:

The subjects of the oral group A1 receive daily 50 mg KLH orally for ten days, followed by two parenteral immunizations with 0.1 mg KLH subcutaneously The subjects of the control group K1 receive only the parenteral immunizations. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Arm type	Active comparator
Investigational medicinal product name	Keyhole limpet hemocyanin (KLH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/skin-prick test
Routes of administration	Cutaneous use

Dosage and administration details:

The subjects of the oral group A1 receive daily 50 mg KLH orally for ten days, followed by two parenteral immunizations with 0.1 mg KLH subcutaneously The subjects of the control group K1 receive only the parenteral immunizations. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Arm title	parenteral-oral-parenteral (A2)

Arm description:

To test whether oral KLH can modulate existing KLH-specific immunity, subjects of groups A2 and K2 are first immunized by two parenteral immunizations with 0.1 mg KLH subcutaneously. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally. The A2 subjects but not the K2 subjects then receive daily 50 mg KLH orally for ten days. Ten days later in both groups a skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Arm type	Experimental
Investigational medicinal product name	Keyhole limpet hemocyanin (KLH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Solution for injection/skin-prick test
Routes of administration	Cutaneous use, Oral use

Dosage and administration details:

To test whether oral KLH can modulate existing KLH-specific immunity, subjects of groups A2 and K2 are first immunized by two parenteral immunizations with 0.1 mg KLH subcutaneously. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally. The A2 subjects but not the K2 subjects then receive daily 50 mg KLH orally for ten days. Ten days later in both groups a skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Arm title	control K2

Arm description:

To test whether oral KLH can modulate existing KLH-specific immunity, subjects of groups A2 and K2 are first immunized by two parenteral immunizations with 0.1 mg KLH subcutaneously. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally. The A2 subjects but not the K2 subjects then receive daily 50 mg KLH orally for ten days. Ten days later in both groups a skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Arm type	Active comparator
Investigational medicinal product name	Keyhole limpet hemocyanin (KLH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/skin-prick test
Routes of administration	Cutaneous use

Dosage and administration details:

To test whether oral KLH can modulate existing KLH-specific immunity, subjects of groups A2 and K2 are first immunized by two parenteral immunizations with 0.1 mg KLH subcutaneously. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally. The A2 subjects but not the K2 subjects then receive daily 50 mg KLH orally for ten days. Ten days later in both groups a skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Number of subjects in period 1	oral-parenteral (A1)	control K1	parenteral-oral-parenteral (A2)
Started	8	8	2
Completed	8	8	2

Number of subjects in period 1	control K2
Started	4
Completed	4

Baseline characteristics

Reporting groups	
Reporting group title	Exposition

Reporting group description: -

Reporting group values	Exposition	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
Adults (18-69)	22	22	
Gender categorical Units: Subjects			
Female	14	14	
Male	8	8	

End points

End points reporting groups

Reporting group title	oral-parenteral (A1)

Reporting group description:

The subjects of the oral group A1 receive daily 50 mg KLH orally for ten days, followed by two parenteral immunizations with 0.1 mg KLH subcutaneously The subjects of the control group K1 receive only the parenteral immunizations. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Reporting group title	control K1

Reporting group description:

The subjects of the oral group A1 receive daily 50 mg KLH orally for ten days, followed by two parenteral immunizations with 0.1 mg KLH subcutaneously The subjects of the control group K1 receive only the parenteral immunizations. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Reporting group title	parenteral-oral-parenteral (A2)

Reporting group description:

To test whether oral KLH can modulate existing KLH-specific immunity, subjects of groups A2 and K2 are first immunized by two parenteral immunizations with 0.1 mg KLH subcutaneously. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally. The A2 subjects but not the K2 subjects then receive daily 50 mg KLH orally for ten days. Ten days later in both groups a skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Reporting group title	control K2

Reporting group description:

To test whether oral KLH can modulate existing KLH-specific immunity, subjects of groups A2 and K2 are first immunized by two parenteral immunizations with 0.1 mg KLH subcutaneously. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally. The A2 subjects but not the K2 subjects then receive daily 50 mg KLH orally for ten days. Ten days later in both groups a skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Primary: Number of SAR

End point title	Number of SAR

End point description:

End point type	Primary

End point timeframe:

Trial duration

End point values	oral-parenteral (A1)	control K1	parenteral-oral-parenteral (A2)	control K2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	8	2	4
Units: Number of SAR	0	0	0	0

Statistical analyses

Statistical analysis title	Safety of oral KLH

Statistical analysis description:

The frequency of SAR will be compared between oral (A1, A2) and parenteral only (K1, K2) groups by the two-tailed Chi-Square test.

Comparison groups	oral-parenteral (A1) v control K1 v parenteral-oral-parenteral (A2) v control K2
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Trial duration

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	oral-parenteral (A1)

Reporting group description:

The subjects of the oral group A1 receive daily 50 mg KLH orally for ten days, followed by two parenteral immunizations with 0.1 mg KLH subcutaneously The subjects of the control group K1 receive only the parenteral immunizations. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Reporting group title	control K1

Reporting group description:

The subjects of the oral group A1 receive daily 50 mg KLH orally for ten days, followed by two parenteral immunizations with 0.1 mg KLH subcutaneously The subjects of the control group K1 receive only the parenteral immunizations. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Reporting group title	parenteral-oral-parenteral (A2)

Reporting group description:

To test whether oral KLH can modulate existing KLH-specific immunity, subjects of groups A2 and K2 are first immunized by two parenteral immunizations with 0.1 mg KLH subcutaneously. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally. The A2 subjects but not the K2 subjects then receive daily 50 mg KLH orally for ten days. Ten days later in both groups a skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Reporting group title	control K2

Reporting group description:

To test whether oral KLH can modulate existing KLH-specific immunity, subjects of groups A2 and K2 are first immunized by two parenteral immunizations with 0.1 mg KLH subcutaneously. A skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally. The A2 subjects but not the K2 subjects then receive daily 50 mg KLH orally for ten days. Ten days later in both groups a skin delayed-type hypersensitivity reaction is elicited by 0.01 mg KLH intradermally.

Serious adverse events	oral-parenteral (A1)	control K1	parenteral-oral-parenteral (A2)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	control K2		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)		
number of deaths (all causes)	0		

number of deaths resulting from adverse events			

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

Non-serious adverse events	oral-parenteral (A1)	control K1	parenteral-oral-parenteral (A2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	7 / 8 (87.50%)	2 / 2 (100.00%)
General disorders and administration site conditions			
skin reaction	Additional description: Skin reaction: patients developed a typical local delayed-type hypersensitivity reaction at the injection site after intradermal application of KLH. This reaction was expected and well-tolerated. No systemic allergic reaction was observed.		
subjects affected / exposed	2 / 8 (25.00%)	7 / 8 (87.50%)	2 / 2 (100.00%)
occurrences (all)	2	7	2

Non-serious adverse events	control K2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
General disorders and administration site conditions			
skin reaction	Additional description: Skin reaction: patients developed a typical local delayed-type hypersensitivity reaction at the injection site after intradermal application of KLH. This reaction was expected and well-tolerated. No systemic allergic reaction was observed.		
subjects affected / exposed	4 / 4 (100.00%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2013	a) non-substantial changes of the protocol (The protocol refers now to the reference values of the Charité Laboratory) b) Amendment with respect to the IMPD (shelf life extension of the IMP)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported