



Clinical trial results:

Comparison of the bacterial microbiota in the skin and gut of psoriasis patients before and after systemic treatment with adalimumab and ustekinumab or cyclosporin

Summary

EudraCT number	2014-003022-40
Trial protocol	DE
Global end of trial date	11 September 2017

Results information

Result version number	v1 (current)
This version publication date	23 September 2018
First version publication date	23 September 2018

Trial information

Trial identification

Sponsor protocol code	UKM14_0008
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1159-2065

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Münster
Sponsor organisation address	Albert-Schweitzer Campus 1, Münster, Germany, 48149
Public contact	Hautklinik, Universitätsklinikum Münster, +49 2518352953, Karin.Loser@ukmuenster.de
Scientific contact	Hautklinik, Universitätsklinikum Münster, +49 2518352953, Karin.Loser@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	11 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 September 2017
Global end of trial reached?	Yes
Global end of trial date	11 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Change in the composition of the cutaneous microbiota in lesional skin of psoriasis patients after systemic treatment with adalimumab, ustekinumab or cyclosporine (baseline versus 4 weeks after start of treatment).

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.

All included participants of the clinical trial are covered by a volunteers' trial insurance according to § 40 AMG (insured as part of a group insurance plan of the Uniklinik Münster).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2015
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: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	37
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between June 2015 and September 2017, about 100 subjects with a moderate to severe Psoriasis were recruited at the outpatient clinic of the Department of Dermatology (University Hospital of Muenster) and referred to the Central Study Coordination for innovative Dermatology (ZID) of the Department of Dermatology (University Hospital of Muenster).

Pre-assignment

Screening details:

At the ZID, 37 were positively screened for moderate to severe psoriasis with a need for systemic therapy and included to the study. Due to a drop out before therapy, one patient was excluded from the trial. The remaining 36 patients were evenly split to the treatment arms. One patient (PASI <10) did not meet the screening criteria but was included

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	Humira
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen, Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Initial dose of 80 mg, followed by 40 mg given every other week starting 1 week after initial dose.

Arm title	Ciclosporin
------------------	-------------

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Ciclosporin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Initial dose 2.5 - 3 mg/kg/day orally. If no improvement, the daily dose can be increased to a max. 5.0 mg/kg/day (dosage usage and administration according to the guidelines for the treatment of Psoriasis vulgaris and the package leaflet)

Arm title	Ustekinumab
------------------	-------------

Arm description: -

Arm type	Active comparator
----------	-------------------

Investigational medicinal product name	Ustekinumab
Investigational medicinal product code	Stelara
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter.

Number of subjects in period 1	Adalimumab	Ciclosporin	Ustekinumab
Started	12	12	12
Completed	7	8	6
Not completed	5	4	7
Physician decision	2	1	-
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	1	3	2
Lost to follow-up	1	-	2
Lack of efficacy	1	-	-
Protocol deviation	-	-	2
Joined	0	0	1
Late recruitment	-	-	1
Late recruitment reason			One patient dropped out before receiving any medication due to lost to follow up

Baseline characteristics

Reporting groups

Reporting group title	Adalimumab
Reporting group description: -	
Reporting group title	Ciclosporin
Reporting group description: -	
Reporting group title	Ustekinumab
Reporting group description: -	

Reporting group values	Adalimumab	Ciclosporin	Ustekinumab
Number of subjects	12	12	13
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	12	12	13
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	44	40	46
standard deviation	± 13	± 13	± 12
Gender categorical			
Units: Subjects			
Female	2	4	5
Male	10	8	8
PASI			
Psoriasis area severity index			
Units: unit(s)			
arithmetic mean	15.4	17.2	14.4
standard deviation	± 7.0	± 7.7	± 5.2
BSA			
Body surface area			
Units: percent			
arithmetic mean	16.3	21.8	13.3
standard deviation	± 13.1	± 15.8	± 6.5
Weight			
Units: kilogram(s)			
arithmetic mean	93.8	88.8	100.5
standard deviation	± 14.3	± 33.7	± 21.4
Reporting group values	Total		

Number of subjects	37		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	37		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	11		
Male	26		
PASI			
Psoriasis area severity index			
Units: unit(s)			
arithmetic mean			
standard deviation	-		
BSA			
Body surface area			
Units: percent			
arithmetic mean			
standard deviation	-		
Weight			
Units: kilogram(s)			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Adalimumab
Reporting group description: -	
Reporting group title	Ciclosporin
Reporting group description: -	
Reporting group title	Ustekinumab
Reporting group description: -	
Subject analysis set title	Cutaneous microbiome before treatment
Subject analysis set type	Full analysis
Subject analysis set description:	
The analysis set includes all available samples regardless of skin site (limb or trunk) or if the subjects completed the full therapy regime.	
To acquire the relative abundances of the main cutaneous phyla in the lesional skin, all untreated subjects of the 3 treatment arms (Adalimumab, Ciclosporin and Ustekinumab) have been combined.	
Subject analysis set title	Intestinal microbiome before treatment
Subject analysis set type	Full analysis
Subject analysis set description:	
The analysis set includes all available samples (subjects who completed the full therapy regimes and drop outs).	
To acquire the relative abundances of the main phyla of the intestine, all untreated subjects of the 3 treatment arms (Adalimumab, Ciclosporin and Ustekinumab) have been combined.	

Primary: Lesional skin microbiota at baseline

End point title	Lesional skin microbiota at baseline ^[1]
End point description:	
Relative Abundances of the main phyla of the cutaneous microbiome of all subjects who participated in the study, regardless of body site (limp or trunk) or successful completion of the therapy regime.	
End point type	Primary
End point timeframe:	
Baseline: before systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.	

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: As an explorative pilot study utilising only a small number of subjects, the results are not to be interpreted in a confirmatory sense but are meant to generate initial hypotheses.

End point values	Cutaneous microbiome before treatment			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	4.3 (± 5.5)			
Firmicutes	45.2 (± 17.3)			
Proteobacteria	20.6 (± 12.3)			
Actinobacteria	22.4 (± 8.9)			
Other	7.6 (± 10.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Lesional skin microbiota after 4 weeks of treatment

End point title | Lesional skin microbiota after 4 weeks of treatment^[2]

End point description:

Relative abundances of the main phyla of the cutaneous microbiome of all subjects who participated in the study, regardless of body site (limb or trunk) or successful completion of the therapy regime.

End point type | Primary

End point timeframe:

4 weeks after systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

Notes:

[2] - 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: As an explorative pilot study utilising only a small number of subjects, the results are not to be interpreted in a confirmatory sense but are meant to generate initial hypotheses.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	12	12	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	4.0 (± 2.5)	2.8 (± 4.3)	4.2 (± 5.4)	
Firmicutes	43.9 (± 20.2)	45.0 (± 15.7)	39.0 (± 23.3)	
Proteobacteria	24.3 (± 14.3)	19.5 (± 7.5)	25.8 (± 18.4)	
Actinobacteria	23.9 (± 9.6)	28.2 (± 14.7)	26.0 (± 14.4)	
Other	4.0 (± 3.7)	4.5 (± 4.7)	4.9 (± 5.7)	

Statistical analyses

No statistical analyses for this end point

Primary: Lesional skin microbiota at baseline - Limb

End point title | Lesional skin microbiota at baseline - Limb^[3]

End point description:

This analysis only includes subjects with the sample site at the limbs and who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).

End point type | Primary

End point timeframe:

Baseline: before systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

Notes:

[3] - 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: As an explorative pilot study utilising only a small number of subjects, the results are not to be interpreted in a confirmatory sense but are meant to generate initial hypotheses.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	4	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	3.0 (± 2.4)	2.1 (± 2.2)	3.3 (± 5.5)	
Firmicutes	28.8 (± 4.8)	45.7 (± 15.7)	45.6 (± 21.6)	
Proteobacteria	32.5 (± 9.1)	14.2 (± 9.0)	23.0 (± 21.6)	
Actinobacteria	27.6 (± 7.0)	21.3 (± 6.9)	23.8 (± 8.7)	
Other	8.1 (± 8.0)	16.6 (± 22.7)	4.2 (± 3.7)	

Statistical analyses

No statistical analyses for this end point

Primary: Lesional skin microbiota after 4 weeks of treatment - Limb

End point title	Lesional skin microbiota after 4 weeks of treatment - Limb ^[4]
-----------------	---

End point description:

This analysis only includes subjects with the sample site at the limbs and who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).

End point type	Primary
----------------	---------

End point timeframe:

4 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

Notes:

[4] - 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: As an explorative pilot study utilising only a small number of subjects, the results are not to be interpreted in a confirmatory sense but are meant to generate initial hypotheses.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	2	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	3.4 (± 2.6)	0 (± 0)	1.3 (± 1.9)	
Firmicutes	33.8 (± 13.2)	53.2 (± 18.6)	32.2 (± 0.8)	
Proteobacteria	33.2 (± 15.8)	20.3 (± 8.9)	18.9 (± 20.4)	
Actinobacteria	26.2 (± 5.9)	22.4 (± 12.1)	45.8 (± 22.7)	
Other	3.4 (± 1.1)	4.2 (± 3.3)	1.8 (± 0.3)	

Statistical analyses

No statistical analyses for this end point

Primary: Lesional skin microbiota at baseline - Trunk

End point title	Lesional skin microbiota at baseline - Trunk ^[5]
End point description:	This analysis only includes subjects with the sample site at the trunk and who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).
End point type	Primary
End point timeframe:	Baseline: before systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

Notes:

[5] - 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: As an explorative pilot study utilising only a small number of subjects, the results are not to be interpreted in a confirmatory sense but are meant to generate initial hypotheses.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	2	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	2.9 (± 5.0)	0.6 (± 0.9)	7.6 (± 10.7)	
Firmicutes	48.5 (± 1.8)	42.3 (± 30.6)	39.6 (± 29.5)	
Proteobacteria	21.3 (± 7.8)	21.4 (± 13.4)	20.5 (± 18.9)	
Actinobacteria	21.8 (± 3.9)	30.7 (± 12.4)	29.6 (± 1.8)	
Other	5.5 (± 3.3)	5.0 (± 5.7)	2.7 (± 1.7)	

Statistical analyses

No statistical analyses for this end point

Primary: Lesional skin microbiota after 4 weeks of treatment - Trunk

End point title	Lesional skin microbiota after 4 weeks of treatment - Trunk ^[6]
End point description:	This analysis only includes subjects with the sample site at the trunk and who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).
End point type	Primary
End point timeframe:	4 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

Notes:

[6] - 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: As an explorative pilot study utilising only a small number of subjects, the results are not to be interpreted in a confirmatory sense but are meant to generate initial hypotheses.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	1	2	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	4.3 (± 3.9)	0 (± 0)	0 (± 0)	
Firmicutes	43.7 (± 10.0)	20.2 (± 0)	40.8 (± 40.9)	
Proteobacteria	23.6 (± 0.2)	15.9 (± 0)	28.3 (± 37.3)	
Actinobacteria	21.0 (± 2.1)	62.0 (± 0)	29.5 (± 2.8)	
Other	7.4 (± 8.0)	1.9 (± 0)	1.3 (± 0.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lesional skin microbiota after 12 weeks of treatment

End point title	Lesional skin microbiota after 12 weeks of treatment
-----------------	--

End point description:

Relative abundances of the main phyla of the cutaneous microbiome of all subjects who participated in the study, regardless of body site (limp or trunk) or successful completion of the therapy regime.

End point type	Secondary
----------------	-----------

End point timeframe:

12 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	12	9	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	4.4 (± 3.8)	2.4 (± 3.1)	6.2 (± 10.4)	
Firmicutes	39.1 (± 15.1)	44.2 (± 11.7)	35.9 (± 25.6)	
Proteobacteria	29.1 (± 15.7)	20.2 (± 10.4)	30.1 (± 16.3)	
Actinobacteria	22.5 (± 4.5)	28.1 (± 13.9)	23.5 (± 11.0)	
Other	5.0 (± 4.1)	5.1 (± 2.0)	4.4 (± 3.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lesional skin microbiota after 24 weeks of treatment

End point title	Lesional skin microbiota after 24 weeks of treatment
-----------------	--

End point description:

Relative abundances of the main phyla of the cutaneous microbiome of all subjects who participated in the study, regardless of body site (limp or trunk) or successful completion of the therapy regime.

End point type	Secondary
End point timeframe:	
24 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.	

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	7	7	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	3.5 (± 2.9)	1.7 (± 3.2)	1.5 (± 2.1)	
Firmicutes	33.1 (± 17.9)	46.5 (± 15.2)	42.0 (± 21.5)	
Proteobacteria	33.8 (± 23.0)	17.1 (± 11.0)	21.6 (± 11.9)	
Actinobacteria	21.0 (± 9.0)	33.0 (± 21.0)	30.3 (± 8.4)	
Other	8.6 (± 11.0)	1.8 (± 0.7)	4.5 (± 3.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Healthy skin microbiota at baseline - Limb

End point title	Healthy skin microbiota at baseline - Limb
End point description:	
This analysis only includes subjects with the sample site at the limbs and who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).	
End point type	Secondary
End point timeframe:	
Baseline: before systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.	

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	4	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	5.9 (± 7.5)	6.7 (± 14.9)	1.5 (± 3.0)	
Firmicutes	34.6 (± 13.7)	50.2 (± 17.3)	59.2 (± 16.6)	
Proteobacteria	32.9 (± 11.5)	25.6 (± 21.2)	6.9 (± 1.6)	
Actinobacteria	21.8 (± 8.6)	11.2 (± 8.9)	3.2 (± 2.0)	
Other	4.9 (± 4.5)	6.3 (± 8.3)	1.1 (± 0.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Healthy skin microbiota at baseline - Trunk

End point title	Healthy skin microbiota at baseline - Trunk
End point description:	This analysis only includes subjects with the sample site at the trunk and who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).
End point type	Secondary
End point timeframe:	Baseline: before systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	2	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	7.0 (± 6.0)	0.8 (± 1.1)	0 (± 0)	
Firmicutes	42.8 (± 13.0)	49.2 (± 45.6)	45.1 (± 12.8)	
Proteobacteria	22.8 (± 6.3)	12.4 (± 17.5)	11.6 (± 11.9)	
Actinobacteria	19.8 (± 9.5)	35.3 (± 25.1)	37.8 (± 0.9)	
Other	7.6 (± 4.3)	2.4 (± 1.9)	5.5 (± 1.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lesional skin microbiota after 12 weeks of treatment - Limb

End point title	Lesional skin microbiota after 12 weeks of treatment - Limb
End point description:	This analysis only includes subjects with the sample site at the limbs and who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).
End point type	Secondary
End point timeframe:	12 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	4	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	5.0 (± 5.2)	2.0 (± 3.1)	9.1 (± 14.5)	
Firmicutes	27.5 (± 4.1)	47.3 (± 5.1)	26.7 (± 11.9)	
Proteobacteria	38.2 (± 13.5)	20.5 (± 11.5)	36.5 (± 18.0)	

Actinobacteria	24.9 (± 3.1)	25.7 (± 16.5)	25.8 (± 8.3)	
Other	4.4 (± 4.6)	4.5 (± 1.7)	1.9 (± 1.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lesional skin microbiota after 24 weeks of treatment - Limb

End point title	Lesional skin microbiota after 24 weeks of treatment - Limb
-----------------	---

End point description:

This analysis only includes subjects with the sample site at the limbs and who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).

End point type	Secondary
----------------	-----------

End point timeframe:

24 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	5	4	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	3.1 (± 1.4)	0.9 (± 1.4)	2.3 (± 2.6)	
Firmicutes	27.5 (± 20.8)	50.7 (± 9.1)	36.9 (± 9.3)	
Proteobacteria	38.7 (± 29.3)	20.6 (± 12.9)	25.6 (± 10.2)	
Actinobacteria	18.8 (± 10.2)	25.8 (± 12.3)	32.2 (± 0.9)	
Other	11.8 (± 15.2)	2.2 (± 0.6)	3.0 (± 1.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lesional skin microbiota after 12 weeks of treatment - Trunk

End point title	Lesional skin microbiota after 12 weeks of treatment - Trunk
-----------------	--

End point description:

This analysis only includes subjects with the sample site at the trunk and who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).

End point type	Secondary
----------------	-----------

End point timeframe:

12 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	2	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	4.5 (± 2.4)	0 (± 0)	1.9 (± 0.8)	
Firmicutes	45.8 (± 9.2)	27.5 (± 16.7)	29.2 (± 19.5)	
Proteobacteria	23.4 (± 13.8)	21.9 (± 15.3)	32.3 (± 9.0)	
Actinobacteria	19.4 (± 5.4)	47.2 (± 1.1)	30.5 (± 12.1)	
Other	6.8 (± 4.0)	3.4 (± 2.5)	6.1 (± 0.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Lesional skin microbiota after 24 weeks of treatment - Trunk

End point title	Lesional skin microbiota after 24 weeks of treatment - Trunk
-----------------	--

End point description:

This analysis only includes subjects with the sample site at the trunk and who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).

End point type	Secondary
----------------	-----------

End point timeframe:

24 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	2	2	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	2.2 (± 2.7)	0 (± 0)	0.8 (± 1.1)	
Firmicutes	32.5 (± 11.5)	30.8 (± 24.4)	32.7 (± 26.6)	
Proteobacteria	34.0 (± 17.4)	10.3 (± 2.9)	23.6 (± 8.9)	
Actinobacteria	24.6 (± 9.7)	58.0 (± 27.8)	34.9 (± 9.6)	
Other	6.7 (± 4.8)	0.9 (± 0.5)	8.1 (± 7.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Intestinal microbiome at baseline

End point title	Intestinal microbiome at baseline
End point description: Relative abundances of the main phyla of the intestinal microbiome of all subjects who participated in the study, regardless of successful completion of the therapy regime.	
End point type	Secondary
End point timeframe: Baseline: before systemic treatment with Adalimumab, Ciclosporin or Ustekinumab	

End point values	Intestinal microbiome before treatment			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	41.2 (± 10.8)			
Firmicutes	40.5 (± 10.1)			
Proteobacteria	11.0 (± 9.3)			
Actinobacteria	3.5 (± 3.4)			
Verrucomicrobia	1.8 (± 4.0)			
Other	2.1 (± 3.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intestinal microbiome after 4 weeks of treatment

End point title	Intestinal microbiome after 4 weeks of treatment
End point description: Relative abundances of the main phyla of the intestinal microbiome of all subjects who participated in the study, regardless of successful completion of the therapy regime.	
End point type	Secondary
End point timeframe: 4 weeks after systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.	

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	10	10	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	37.5 (± 11.8)	35.6 (± 10.2)	36.9 (± 15.8)	
Firmicutes	44.9 (± 16.3)	35.2 (± 12.1)	44.8 (± 20.1)	

Proteobacteria	8.6 (± 6.7)	16.3 (± 11.6)	11.5 (± 11.6)	
Actinobacteria	4.9 (± 4.6)	2.4 (± 3.5)	5.3 (± 6.2)	
Verrucomicrobia	1.5 (± 4.1)	2.8 (± 4.1)	0 (± 0)	
Other	2.6 (± 2.7)	7.6 (± 13.2)	1.5 (± 0.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Intestinal microbiome after 12 weeks of treatment

End point title	Intestinal microbiome after 12 weeks of treatment
End point description:	Relative abundances of the main phyla of the intestinal microbiome of all subjects who participated in the study, regardless of successful completion of the therapy regime.
End point type	Secondary
End point timeframe:	12 weeks after systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	7	6	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	37.1 (± 11.6)	41.7 (± 6.3)	37.7 (± 7.2)	
Firmicutes	40.8 (± 11.5)	38.9 (± 6.6)	38.5 (± 10.4)	
Proteobacteria	7.5 (± 7.2)	9.9 (± 7.6)	19.0 (± 9.1)	
Actinobacteria	3.8 (± 5.5)	2.9 (± 3.2)	4.2 (± 5.8)	
Verrucomicrobia	0.2 (± 0.5)	3.9 (± 6.7)	4.2 (± 7.5)	
Other	10.5 (± 15.0)	2.6 (± 3.0)	1.2 (± 1.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Intestinal microbiome after 24 weeks of treatment

End point title	Intestinal microbiome after 24 weeks of treatment
End point description:	Relative abundances of the main phyla of the intestinal microbiome of all subjects who participated in the study, regardless of successful completion of the therapy regime.
End point type	Secondary
End point timeframe:	24 weeks after systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	4	4	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	37.8 (± 11.8)	44.5 (± 8.3)	46.4 (± 6.3)	
Firmicutes	36.0 (± 11.8)	37.8 (± 9.6)	40.2 (± 4.9)	
Proteobacteria	11.5 (± 5.2)	8.0 (± 5.1)	8.7 (± 5.9)	
Actinobacteria	3.3 (± 4.4)	3.8 (± 6.0)	1.4 (± 1.7)	
Verrucomicrobia	2.5 (± 2.8)	4.6 (± 7.4)	1.4 (± 2.8)	
Other	8.8 (± 10.5)	1.2 (± 0.4)	1.9 (± 1.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Intestinal microbiome at baseline (without drop outs)

End point title	Intestinal microbiome at baseline (without drop outs)
-----------------	---

End point description:

This analysis only includes subjects who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline: before systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	37.0 (± 7.1)	45.9 (± 6.9)	51.0 (± 10.0)	
Firmicutes	35.7 (± 4.6)	40.1 (± 3.0)	35.9 (± 7.4)	
Proteobacteria	11.7 (± 3.0)	5.5 (± 4.3)	10.6 (± 5.6)	
Verrucomicrobia	5.9 (± 6.9)	4.1 (± 5.9)	0 (± 0)	
Actinobacteria	3.9 (± 3.7)	1.7 (± 1.5)	0.3 (± 0.6)	
Other	5.8 (± 8.1)	2.6 (± 2.3)	2.2 (± 3.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Intestinal microbiome after 4 weeks of treatments (without drop outs)

End point title	Intestinal microbiome after 4 weeks of treatments (without drop outs)
-----------------	---

End point description:

This analysis only includes subjects who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).

End point type	Secondary
----------------	-----------

End point timeframe:

4 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	4	3	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	42.4 (± 6.7)	42.6 (± 4.7)	42.2 (± 5.6)	
Firmicutes	37.1 (± 5.8)	38.4 (± 6.4)	45.8 (± 4.2)	
Proteobacteria	11.0 (± 7.0)	10.3 (± 10.7)	10.4 (± 3.8)	
Verrucomicrobia	3.6 (± 6.2)	2.9 (± 4.3)	0 (± 0)	
Actinobacteria	1.8 (± 0.7)	2.6 (± 2.2)	0.4 (± 0.6)	
Other	4.1 (± 3.9)	3.3 (± 2.8)	1.2 (± 0.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Intestinal microbiome after 12 weeks of treatments (without drop outs)

End point title	Intestinal microbiome after 12 weeks of treatments (without drop outs)
-----------------	--

End point description:

This analysis only includes subjects who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).

End point type	Secondary
----------------	-----------

End point timeframe:

12 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	3	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	44.4 (± 8.4)	39.8 (± 6.9)	37.5 (± 6.9)	
Firmicutes	39.9 (± 6.9)	40.6 (± 8.6)	43.9 (± 10.4)	
Proteobacteria	6.0 (± 6.0)	8.9 (± 9.6)	16.6 (± 13.1)	
Verrucomicrobia	0.4 (± 0.7)	4.6 (± 9.2)	0 (± 0)	
Actinobacteria	1.4 (± 0.1)	2.2 (± 1.7)	0.5 (± 0.8)	
Other	7.9 (± 11.3)	4.1 (± 3.4)	1.5 (± 1.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Intestinal microbiome after 24 weeks of treatments (without drop outs)

End point title	Intestinal microbiome after 24 weeks of treatments (without drop outs)
-----------------	--

End point description:

This analysis only includes subjects who completed the full treatment regime (24 weeks of Adalimumab, Ciclosporin or Ustekinumab).

End point type	Secondary
----------------	-----------

End point timeframe:

24 weeks after systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	33.0 (± 7.8)	44.5 (± 8.3)	46.4 (± 6.3)	
Firmicutes	37.3 (± 10.6)	37.8 (± 9.6)	40.2 (± 4.9)	
Proteobacteria	12.6 (± 2.1)	8.0 (± 5.1)	8.7 (± 5.9)	
Verrucomicrobia	3.8 (± 2.6)	4.2 (± 7.5)	1.4 (± 2.8)	
Actinobacteria	2.1 (± 1.8)	4.2 (± 5.8)	1.4 (± 1.7)	
Other	11.2 (± 12.6)	1.2 (± 0.4)	1.9 (± 1.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: PASI (end of trial)

End point title	PASI (end of trial)
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.	

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	6	
Units: unit(s)				
arithmetic mean (standard deviation)				
PASI	3.9 (± 8.0)	5.9 (± 5.2)	2.6 (± 3.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: BSA (end of trial)

End point title	BSA (end of trial)
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks of systemic treatment with Adalimumab, Ciclosporin or Ustekinumab.	

End point values	Adalimumab	Ciclosporin	Ustekinumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	6	
Units: percent				
arithmetic mean (standard deviation)				
BSA	6.1 (± 10.5)	5.6 (± 3.7)	5.3 (± 7.9)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The timeframe for adverse event reporting is max. 24 weeks (completion of the full treatment regime).

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	20.1
--------------------	------

Reporting groups

Reporting group title	Adalimumab
-----------------------	------------

Reporting group description: -

Reporting group title	Ciclosporin
-----------------------	-------------

Reporting group description: -

Reporting group title	Ustekinumab
-----------------------	-------------

Reporting group description: -

Serious adverse events	Adalimumab	Ciclosporin	Ustekinumab
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	1 / 12 (8.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Condition aggravated	Additional description: Worsening of chronic venous insufficiency		
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Adalimumab	Ciclosporin	Ustekinumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 12 (50.00%)	10 / 12 (83.33%)	9 / 12 (75.00%)
Investigations			
Biopsy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Occult blood			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Post-traumatic pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Peripheral venous disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Surgical and medical procedures			
Skin neoplasm excision			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Wisdom teeth removal			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 12 (16.67%) 2	0 / 12 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Gastrointestinal disorders			
Gingival bleeding subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 12 (16.67%) 2	0 / 12 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 12 (16.67%) 2	1 / 12 (8.33%) 1
Crohn's disease subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 12 (16.67%) 2	0 / 12 (0.00%) 0
Gingival hypertrophy subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Abdominal discomfort			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Skin and subcutaneous tissue disorders			
Actinic keratosis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Alopecia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Rash subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0
Skin striae subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Psoriasis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Joint effusion subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Arthralgia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0
Spinal pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1
Infections and infestations			

Tonsillitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pulpitis dental			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	3 / 12 (25.00%)	5 / 12 (41.67%)	1 / 12 (8.33%)
occurrences (all)	5	8	1
Bronchitis bacterial			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Bacterial infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Viral tonsillitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Lice infestation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Herpes simplex			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Increased appetite			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2015	<ul style="list-style-type: none">- Sampling of healthy skin and biopsies only taken at baseline before treatment. Reasoning: No changes of the microbiome in healthy skin is to be expected due to systemic therapy - Biopsie wounds are closed by suture instead of using a patch: Reasoning: for the best possible cosmetic result
18 December 2015	<ul style="list-style-type: none">- Adjustment of exclusion criteria for all patients: Prophylaxis of tuberculosis using Isoniazid is no longer an exclusion criteria: Reasoning: effect of Isoniazid treatment is selective for mycobacterium tuberculosis and mycobacterium bovis. No impact on the study results is to be expected. Subjects with latent tuberculosis or with a history of latent or active tuberculosis without proof of an adequate treatment can be included in the study - Additional exclusion of subjects which are positive for the hepatitis-C virus (HPV-PCR positive) for safety reasons - For safety reasons while in treatment with Adalimumab or Ustekinumab: subjects with latent tuberculosis or with a history of latent or active tuberculosis without proof of an adequate treatment and subjects with several or significant risk factors for tuberculosis have to be additionally treated with a tuberculosis prophylaxis. - Deletion of an additional exclusion criteria for subjects of the ciclosporin treatment arm: Deleted exclusion Criteria 10: long-term treatment with methotrexate Reasoning: Criteria missing in the updated product characteristics of Immunosporin® soft capsules 07/2015 - Determination of the Estimated Glomerular Filtration Rate (eGFR) introduced to the monitoring of the patients during the visits of Ciclosporin treated subjects In case of an decreasing eGFR: adjustments to the dosage based on recommendations given in the updated product characteristics of Immunosporin® soft capsules 07/2015 Reasoning: Recommendation of the updated product characteristics of Immunosporin® soft capsules 07/2015

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported