



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