



Clinical trial results:

Remission in rheumatoid arthritis – assessing withdrawal of disease-modifying antirheumatic drugs in a non-inferiority design (Analyses of patients who receive tumor necrosis factor inhibitor drugs (TNFi))

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-005275-14 |
| Trial protocol | NO |
| Global end of trial date | 23 March 2022 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 19 November 2023 |
| First version publication date | 19 November 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | DIA2012-1 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01881308 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Diakonhjemmet Hospital AS |
| Sponsor organisation address | Diakonveien 12, Oslo, Norway, 0370 |
| Public contact | Principal Investigator, Diakonhjemmet Hospital AS, +47 22451500, e.a.haavardsholm@medisin.uio.no |
| Scientific contact | Principal Investigator, Diakonhjemmet Hospital AS, +47 22451500, e.a.haavardsholm@medisin.uio.no |

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 | 16 January 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 January 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 March 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of tapering and withdrawal of TNFi on disease activity in RA patients in sustained remission.

Protection of trial subjects:

Each patient was instructed to contact the investigator immediately if they showed signs or symptoms they perceived as serious adverse events.

If the patient suspected a flare in disease activity, he or she was instructed to contact the study site immediately and they should be seen within a week.

Patients had the right to withdraw from the study at any time for any reason.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------------------------------|
| Actual start date of recruitment | 06 December 2013 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy, Scientific research |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Norway: 99 |
| Worldwide total number of subjects | 99 |
| EEA total number of subjects | 99 |

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) | 63 |

| | |
|---------------------|----|
| From 65 to 84 years | 30 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details:

Enrolment of patients took place at nine hospital-based rheumatology practices in Norway

Pre-assignment

Screening details:

Adult men and women with RA who had been in sustained remission for at least 1 year on stable TNFi medication were screened by a study investigator (physician) for inclusion into the study.

Period 1

| | |
|------------------------------|-------------------------------|
| Period 1 title | intervention (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Tapering of TNFi |

Arm description:

tapering of TNFi treatment.

the TNFi was reduced to half dose for 4 months, and withdrawn at the 4-month visit if the patient was still in remission.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | etanercept |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled injector, Solution for injection in pre-filled pen |
| Routes of administration | Injection |

Dosage and administration details:

standard full dosage: 50 mg weekly subcutaneous injection

1/2 dosage regime 25 mg weekly subcutaneous injection

after 4 months discontinued intervention if still in remission.

| | |
|--|--|
| Investigational medicinal product name | certolizumab pegol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Injection |

Dosage and administration details:

Standard dose: 200mg bi-weekly injection.

1/2 dosage regime: 200 mg every 4 week

Discontinuation of intervention at 4 months if still in remission.

| | |
|--|--|
| Investigational medicinal product name | golimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Injection |

Dosage and administration details:

Standard dosage: 50 mg subcutaneous injection every 4 weeks.

1/2 dosage regimen: 50 mg subcutaneous injection every 8 weeks.

Discontinuation after 4 months if still in remission

| | |
|--|------------|
| Investigational medicinal product name | infliximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion |

Dosage and administration details:

Standard full dosage: 3-5 mg/kg intravenous administration every 8 weeks

1/2 dosage regimen: 1.5-3 mg/kg intravenous administration every 8 weeks

Discontinuation at the 4 month visit if still in remission

| | |
|--|--|
| Investigational medicinal product name | adalimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Injection |

Dosage and administration details:

Standard full dosage: 40 mg subcutaneous injection bi-weekly

1/2 dosage regimen: 40 mg subcutaneous injection every 4 weeks

Discontinuation at the 4 month visit if still in remission

| | |
|------------------|-------------|
| Arm title | Stable TNFi |
|------------------|-------------|

Arm description:

patients randomized to continue stable TNFi treatment.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | certolizumab pegol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Injection |

Dosage and administration details:

Standard dose: 200mg bi-weekly injection.

| | |
|--|---|
| Investigational medicinal product name | etanercept |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled injector, Solution for injection in pre-filled pen |
| Routes of administration | Injection |

Dosage and administration details:

standard full dosage: 50 mg weekly subcutaneous injection

| | |
|--|--|
| Investigational medicinal product name | golimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection in pre-filled syringe |
| Routes of administration | Injection |

Dosage and administration details:

Standard dosage: 50 mg subcutaneous injection every 4 weeks.

| | |
|--|------------|
| Investigational medicinal product name | infliximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion |

Dosage and administration details:

Standard full dosage: 3-5 mg/kg intravenous administration every 8 weeks

| | |
|--|--|
| Investigational medicinal product name | adalimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Injection |

Dosage and administration details:

Standard full dosage: 40 mg subcutaneous injection bi-weekly

| Number of subjects in period 1^[1] | Tapering of TNFi | Stable TNFi |
|---|------------------|-------------|
| Started | 47 | 45 |
| Completed | 43 | 41 |
| Not completed | 4 | 4 |
| patients decision | 1 | 1 |
| Adverse event, non-fatal | - | 3 |
| Protocol deviation | 3 | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 7 subjects were randomised, but did not receive the allocated treatment strategy (2 subjects decided to withdraw from the study, and 5 subjects did not meet the inclusion criteria (screening failures)). These were not included in the analyses, in accordance with the protocol and the statistical analysis plan.

Baseline characteristics

Reporting groups

| | |
|--|------------------|
| Reporting group title | Tapering of TNFi |
| Reporting group description: tapering of TNFi treatment. the TNFi was reduced to half dose for 4 months, and withdrawn at the 4-month visit if the patient was still in remission. | |
| Reporting group title | Stable TNFi |
| Reporting group description: patients randomized to continue stable TNFi treatment. | |

| Reporting group values | Tapering of TNFi | Stable TNFi | Total |
|--|------------------|-------------|-------|
| Number of subjects | 47 | 45 | 92 |
| 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 57.6 | 57.4 | |
| standard deviation | ± 12.6 | ± 10.7 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 25 | 30 | 55 |
| Male | 22 | 15 | 37 |
| Anticitrullinated peptide | | | |
| Units: Subjects | | | |
| Positive | 36 | 35 | 71 |
| Negative | 11 | 10 | 21 |
| Rheumatoid factor | | | |
| Units: Subjects | | | |
| Positive | 32 | 28 | 60 |
| Negative | 15 | 17 | 32 |
| ACR EULAR Boolean remission | | | |
| Units: Subjects | | | |
| Yes | 38 | 30 | 68 |
| No | 9 | 15 | 24 |
| Tumor necrosis factor inhibitor | | | |
| Units: Subjects | | | |
| Etanercept | 20 | 20 | 40 |

| | | | |
|---|------------|------------|----|
| Certoizumab pegol | 14 | 15 | 29 |
| Golimumab | 1 | 4 | 5 |
| Infliximab | 9 | 0 | 9 |
| Adalimumab | 3 | 6 | 9 |
| Co-medication with csDMARDs | | | |
| Units: Subjects | | | |
| Yes | 42 | 41 | 83 |
| No | 5 | 4 | 9 |
| Co-medication with methotrexate | | | |
| Units: Subjects | | | |
| Yes | 38 | 38 | 76 |
| No | 9 | 7 | 16 |
| Time since first swollen joint | | | |
| Units: year | | | |
| arithmetic mean | 11.9 | 10.0 | |
| standard deviation | ± 6.9 | ± 7.2 | - |
| Disease activity Score (DAS) | | | |
| DAS (range 0-10) includes a 44 swollen joint count, assessment of tender joints by Ritchie Articular Index, the ESR and patients global assessment of disease activity on a VAS 0-100 mm. | | | |
| Units: score 0-10 | | | |
| arithmetic mean | 0.8 | 0.9 | |
| standard deviation | ± 0.3 | ± 0.4 | - |
| Swollen joint count | | | |
| The swollen joint count is the number of swollen joints out of 44 joints assessed | | | |
| Units: 0-44 | | | |
| arithmetic mean | 0.0 | 0.0 | |
| standard deviation | ± 0.0 | ± 0.0 | - |
| Tender joint count (Ritchie Articular Index) | | | |
| The tender joint count is performed by the Ritchie Articular Index assessing tenderness of 26 joint regions, the index ranges 0-3 for individual measures and the sum 0-78 overall | | | |
| Units: 0-78 | | | |
| arithmetic mean | 0.1 | 0.2 | |
| standard deviation | ± 0.2 | ± 0.5 | - |
| ESR | | | |
| Erythrocyte sedimentation rate mm/hour | | | |
| Units: mm/hour | | | |
| median | 7 | 8 | |
| inter-quartile range (Q1-Q3) | 5 to 14 | 5 to 15 | - |
| CRP | | | |
| C-reactive protein | | | |
| Units: mg/dL | | | |
| median | 0.1 | 0.1 | |
| inter-quartile range (Q1-Q3) | 0.1 to 0.3 | 0.1 to 0.2 | - |
| Patient's global assessment | | | |
| self-reported overall assessment of disease activity with use of a VAS range 0-100 mm | | | |
| Units: 0-100 mm | | | |
| median | 3 | 2 | |
| inter-quartile range (Q1-Q3) | 1 to 12 | 1 to 12 | - |
| Physician's global assessment | | | |
| self-reported overall assessment of disease activity with use of a VAS range 0-100 mm | | | |
| Units: 0-100 mm | | | |

| | | | |
|---|--------------|--------------|---|
| median | 0 | 0 | |
| inter-quartile range (Q1-Q3) | 0 to 2 | 0 to 2 | - |
| PROMIS physical function | | | |
| PROMIS 20 item short form range 0-100, with scores lower than 50 indicating disability worse than average | | | |
| Units: range 0-100 | | | |
| median | 52.6 | 51.2 | |
| inter-quartile range (Q1-Q3) | 49.0 to 62.5 | 44.2 to 62.5 | - |
| Total van der Heijde modified Sharp score | | | |
| This method assesses erosions in 16 of each hand and 6 joints of each foot, and joint space narrowing in 15 joints for each hand as well as six joints of each foot. This gives scores for erosions on a scale of 0-280 and joint-space narrowing on a scale of 0-168, thus the total van der Heijde Sharp score range is 0-448 | | | |
| Units: range 0-448 | | | |
| median | 6.5 | 5 | |
| inter-quartile range (Q1-Q3) | 1.5 to 12 | 1.5 to 13.5 | - |
| Total power Doppler SSignal Score | | | |
| Ultrasound examination was performed using a 0-3 semiquantitative scoring system for both grey scale and power Doppler in 32 joint | | | |
| Units: range 0-96 | | | |
| median | 0 | 0 | |
| inter-quartile range (Q1-Q3) | 0 to 0 | 0 to 0 | - |
| Total Grey Scale Score | | | |
| Ultrasound examination was performed using a 0-3 semiquantitative scoring system for both grey scale and power Doppler in 32 joint | | | |
| Units: range 0-96 | | | |
| median | 1 | 1 | |
| inter-quartile range (Q1-Q3) | 0 to 3 | 0 to 3 | - |

Subject analysis sets

| | |
|---|----------------------------------|
| Subject analysis set title | Tapering TNFi (Per protocol set) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| all randomised patients meeting the study entry criteria and with no protocol deviations affecting the treatment efficacy | |
| Subject analysis set title | Stable TNFi (per protocol set) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| all randomised patients meeting the study entry criteria and with no protocol deviations affecting the treatment efficacy | |

| Reporting group values | Tapering TNFi (Per protocol set) | Stable TNFi (per protocol set) | |
|--|----------------------------------|--------------------------------|--|
| Number of subjects | 43 | 41 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years arithmetic mean standard deviation | 57.3 ± 13 | 57.4 ± 11.2 | |
| Gender categorical Units: Subjects | | | |
| Female Male | 23 20 | 26 15 | |
| Anticitrullinated peptide Units: Subjects | | | |
| Positive Negative | 33 10 | 33 8 | |
| Rheumatoid factor Units: Subjects | | | |
| Positive Negative | 30 13 | 25 16 | |
| ACR EULAR Boolean remission Units: Subjects | | | |
| Yes No | 36 7 | 27 14 | |
| Tumor necrosis factor inhibitor Units: Subjects | | | |
| Etanercept Certoizumab pegol Golimumab Infliximab Adalimumab | 19 12 1 9 2 | 18 15 4 0 4 | |
| Co-medication with csDMARDs Units: Subjects | | | |
| Yes No | 38 5 | 38 3 | |
| Co-medication with methotrexate Units: Subjects | | | |
| Yes No | 34 9 | 35 6 | |
| Time since first swollen joint Units: year arithmetic mean standard deviation | 11.7 ± 7.0 | 9.4 ± 6.6 | |
| Disease activity Score (DAS) | | | |
| DAS (range 0-10) includes a 44 swollen joint count, assessment of tender joints by Ritchie articular index, the ESR and patients global assessment of disease activity on a VAS 0-100 mm. | | | |
| Units: score 0-10 arithmetic mean standard deviation | 0.8 ± 0.3 | 0.9 ± 0.4 | |
| Swollen joint count | | | |
| The swollen joint count is the number of swollen joints out of 44 joints assessed | | | |
| Units: 0-44 | | | |

| | | | |
|---|--------------|--------------|--|
| arithmetic mean | 0.0 | 0.0 | |
| standard deviation | ± 0.0 | ± 0.0 | |
| Tender joint count (Ritchie Articular Index) | | | |
| The tender joint count is performed by the Ritchie Articular Index assessing tenderness of 26 joint regions, the index ranges 0-3 for individual measures and the sum 0-78 overall | | | |
| Units: 0-78 | | | |
| arithmetic mean | 0.1 | 0.2 | |
| standard deviation | ± 0.3 | ± 0.5 | |
| ESR | | | |
| Erythrocyte sedimentation rate mm/hour | | | |
| Units: mm/hour | | | |
| median | 7.0 | 8 | |
| inter-quartile range (Q1-Q3) | 5 to 13 | 5 to 15 | |
| CRP | | | |
| C-reactive protein | | | |
| Units: mg/dL | | | |
| median | 0.1 | 0.1 | |
| inter-quartile range (Q1-Q3) | 0.1 to 0.3 | 0.1 to 0.2 | |
| Patient's global assessment | | | |
| self-reported overall assessment of disease activity with use of a VAS range 0-100 mm | | | |
| Units: 0-100 mm | | | |
| median | 3 | 2 | |
| inter-quartile range (Q1-Q3) | 1 to 9 | 1 to 12 | |
| Physician's global assessment | | | |
| self-reported overall assessment of disease activity with use of a VAS range 0-100 mm | | | |
| Units: 0-100 mm | | | |
| median | 0 | 0 | |
| inter-quartile range (Q1-Q3) | 0 to 2 | 0 to 2 | |
| PROMIS physical function | | | |
| PROMIS 20 item short form range 0-100, with scores lower than 50 indicating disability worse than average | | | |
| Units: range 0-100 | | | |
| median | 52.6 | 51.2 | |
| inter-quartile range (Q1-Q3) | 49.0 to 62.5 | 44.2 to 62.5 | |
| Total van der Heijde modified Sharp score | | | |
| This method assesses erosions in 16 of each hand and 6 joints of each foot, and joint space narrowing in 15 joints for each hand as well as six joints of each foot. This gives scores for erosions on a scale of 0-280 and joint-space narrowing on a scale of 0-168, thus the total van der Heijde Sharp score range is 0-448 | | | |
| Units: range 0-448 | | | |
| median | 6.5 | 5.0 | |
| inter-quartile range (Q1-Q3) | 1.5 to 12.5 | 1.5 to 13.0 | |
| Total power Doppler Signal Score | | | |
| Ultrasound examination was performed using a 0-3 semiquantitative scoring system for both grey scale and power Doppler in 32 joint | | | |
| Units: range 0-96 | | | |
| median | 0 | 0 | |
| inter-quartile range (Q1-Q3) | 0 to 0 | 0 to 0 | |
| Total Grey Scale Score | | | |
| Ultrasound examination was performed using a 0-3 semiquantitative scoring system for both grey scale and power Doppler in 32 joint | | | |
| Units: range 0-96 | | | |
| median | 1 | 1 | |

| | | | |
|------------------------------|--------|--------|--|
| inter-quartile range (Q1-Q3) | 0 to 3 | 0 to 3 | |
|------------------------------|--------|--------|--|

| |
|--|
| |
| |

End points

End points reporting groups

| | |
|--|----------------------------------|
| Reporting group title | Tapering of TNFi |
| Reporting group description: tapering of TNFi treatment. the TNFi was reduced to half dose for 4 months, and withdrawn at the 4-month visit if the patient was still in remission. | |
| Reporting group title | Stable TNFi |
| Reporting group description: patients randomized to continue stable TNFi treatment. | |
| Subject analysis set title | Tapering TNFi (Per protocol set) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: all randomised patients meeting the study entry criteria and with no protocol deviations affecting the treatment efficacy | |
| Subject analysis set title | Stable TNFi (per protocol set) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: all randomised patients meeting the study entry criteria and with no protocol deviations affecting the treatment efficacy | |

Primary: Flare rate

| | |
|---|------------|
| End point title | Flare rate |
| End point description: Flare rate in tapered versus stable TNFi treatment. Flare was defined as a combination of DAS above cut-off for remission (1.6), a change in DAS of at least 0.6, and at least two swollen joints, or that both the treating physician and the patient agreed that a clinically significant flare had occurred. | |
| End point type | Primary |
| End point timeframe: 0-12 months | |

| End point values | Tapering of TNFi | Stable TNFi | Tapering TNFi (Per protocol set) | Stable TNFi (per protocol set) |
|-----------------------------|------------------|-----------------|----------------------------------|--------------------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 47 | 45 | 43 | 41 |
| Units: flare | | | | |
| yes | 28 | 4 | 27 | 2 |
| no | 19 | 41 | 16 | 39 |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Difference in flare rate |
| Statistical analysis description: Assess the non-inferiority of tapered TNFi therapy compared to stable TNFi therapy. | |
| Comparison groups | Tapering TNFi (Per protocol set) v Stable TNFi (per protocol set) |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 84 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 57.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 42 |
| upper limit | 73.8 |

Secondary: Progression of radiographic joint damage

| | |
|------------------------|--|
| End point title | Progression of radiographic joint damage |
| End point description: | Progression of radiographic joint damage was defined as a change of ≥ 1 unit per year |
| End point type | Secondary |
| End point timeframe: | 0-12 months |

| End point values | Tapering TNFi (Per protocol set) | Stable TNFi (per protocol set) | | |
|-----------------------------------|-------------------------------------|-----------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 42 | 40 | | |
| Units: van der Heijde Sharp score | | | | |
| number (not applicable) | | | | |
| yes | 8 | 4 | | |
| no | 34 | 36 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease activity remission (DAS)

| | |
|------------------------|---|
| End point title | Disease activity remission (DAS) |
| End point description: | Rate of Disease activity (DAS) remission at 12 months |
| End point type | Secondary |
| End point timeframe: | 12 months |

| End point values | Tapering TNFi (Per protocol set) | Stable TNFi (per protocol set) | | |
|-----------------------------|--|--------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 42 | 40 | | |
| Units: remission | | | | |
| yes | 37 | 34 | | |
| no | 42 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DAS at time of flare

| | |
|---|----------------------|
| End point title | DAS at time of flare |
| End point description: | |
| Disease activity score at time of flare | |
| End point type | Secondary |
| End point timeframe: | |
| time of flare | |

| End point values | Tapering TNFi (Per protocol set) | Stable TNFi (per protocol set) | | |
|------------------------------------|--|--------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 25 | 2 | | |
| Units: disease activity score 0-10 | | | | |
| median (standard error) | 2.2 (± 0.8) | 1.9 (± 0.2) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

0-12 months

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

Dictionary used

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

| | |
|--------------------|--------|
| Dictionary version | V21.1E |
|--------------------|--------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Tapering of TNFi |
|-----------------------|------------------|

Reporting group description:

tapering of TNFi treatment.

the TNFi was reduced to half dose for 4 months, and withdrawn at the 4-month visit if the patient was still in remission.

| | |
|-----------------------|-------------|
| Reporting group title | Stable TNFi |
|-----------------------|-------------|

Reporting group description:

patients randomized to continue stable TNFi treatment.

| Serious adverse events | Tapering of TNFi | Stable TNFi | |
|---|------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 47 (6.38%) | 2 / 45 (4.44%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Falling down | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 45 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Rheumatoid vasculitis | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 1 / 45 (2.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Heart attack | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 45 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|----------------|--|
| atrioventricular block third degree subjects affected / exposed | 0 / 47 (0.00%) | 1 / 45 (2.22%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | 0 / 45 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Tapering of TNFi | Stable TNFi | |
|--|------------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 47 (14.89%) | 5 / 45 (11.11%) | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 47 (0.00%) | 3 / 45 (6.67%) | |
| occurrences (all) | 0 | 3 | |
| Infections and infestations | | | |
| common cold | | | |
| subjects affected / exposed | 7 / 47 (14.89%) | 2 / 45 (4.44%) | |
| occurrences (all) | 7 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 14 December 2017 | The initial protocol required symptom duration less than 5 years; this was removed in a protocol update. The reasons included that some patients could not be included due to difficulties in determining symptom duration, and that the protocol update increased the number of patients eligible for enrolment. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-----------------|--|--------------|
| 04 January 2019 | Patient recruitment was closed before the target number had been reached due to a lower inclusion rate than anticipated. | - |

Notes:

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37607809>