



Clinical trial results:

The Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis Study Comparing the cost-effectiveness and safety of additional low-dose glucocorticoid in treatment strategies for elderly patients with rheumatoid arthritis

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-002729-21 |
| Trial protocol | DE HU SK FI PT |
| Global end of trial date | 28 April 2021 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 05 February 2022 |
| First version publication date | 05 February 2022 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | VUMC-ARC-GLORIA |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02585258 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | VU University Medical Center |
| Sponsor organisation address | de Boelelaan 1117, Amsterdam, Netherlands, 1081 HV |
| Public contact | Project Coordinator, VU University Medical Center, leonie@middelinc.com |
| Scientific contact | Scientific Lead, VU University Medical Center, 31 204444474, m.boers@amsterdamumc.nl |

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 | 29 April 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 February 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 April 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

- a) To assess the effectiveness, safety and cost-effectiveness of 2 years of low-dose GC therapy (5 mg/day) compared to placebo as co-treatment for elderly RA patients in a pragmatic randomized trial
b) Study medication adherence through a medication packaging solution, and test the effectiveness of smart device technology to improve adherence

Protection of trial subjects:

Informed Consent Procedure, trial insurance and no additional assessments than standard of care.

Background therapy:

Standard of care treatment.

Evidence for comparator:

NA

| | |
|---|--------------|
| Actual start date of recruitment | 29 June 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Netherlands: 285 |
| Country: Number of subjects enrolled | Portugal: 26 |
| Country: Number of subjects enrolled | Slovakia: 2 |
| Country: Number of subjects enrolled | Germany: 10 |
| Country: Number of subjects enrolled | Hungary: 12 |
| Country: Number of subjects enrolled | Italy: 60 |
| Country: Number of subjects enrolled | Romania: 56 |
| Worldwide total number of subjects | 451 |
| EEA total number of subjects | 451 |

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) | 0 |
| From 65 to 84 years | 441 |
| 85 years and over | 10 |

Subject disposition

Recruitment

Recruitment details:

From June 2016 to December 2018, 451 patients were randomised in the Gloria trial in 7 European countries, the majority (285) in The Netherlands.

Pre-assignment

Screening details:

Patients of 65 years of age and older with RA according to the 2010 classification criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), requiring antirheumatic therapy because of inadequate disease control, as evidenced by a disease activity score (DAS28) ≥ 2.60 .

Period 1

| | |
|------------------------------|---|
| Period 1 title | Study duration (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Everybody involved in the trial was blinded, except for the unblinded monitor.

Arms

| | |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes |
| Arm title | Active |

Arm description:

1 prednisolone 5 mg capsule / day

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Prednisolon |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

daily 1 capsule

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

1 placebo capsule per day

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

1 placebo capsule per day

| Number of subjects in period 1^[1] | Active | Placebo |
|---|--------|---------|
| Started | 224 | 225 |
| Subjects completed 2 years | 141 | 137 |
| subjects included in safety population | 224 | 225 |
| Completed | 141 | 137 |
| Not completed | 83 | 88 |
| Adverse event, serious fatal | 3 | 2 |
| Consent withdrawn by subject | 42 | 48 |
| Adverse event, non-fatal | 28 | 29 |
| Lost to follow-up | 3 | - |
| Lack of efficacy | 7 | 9 |

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: the baseline characteristics are reported for the safety population (n=449). This excludes two patients in the prednisolone group who withdrew consent and did not start study medication.

Baseline characteristics

Reporting groups

| | |
|---|---------|
| Reporting group title | Active |
| Reporting group description: 1 prednisolone 5 mg capsule / day | |
| Reporting group title | Placebo |
| Reporting group description: 1 placebo capsule per day | |

| Reporting group values | Active | Placebo | Total |
|---|--------|---------|-------|
| Number of subjects | 224 | 225 | 449 |
| 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 | 72.5 | 72.6 | - |
| standard deviation | ± 5.3 | ± 5.4 | |
| Gender categorical Units: Subjects | | | |
| Female | 160 | 156 | 316 |
| Male | 64 | 69 | 133 |
| prior glucocorticoid therapy Units: Subjects | | | |
| prior GC therapy | 105 | 104 | 209 |
| no prior GC therapy | 119 | 121 | 240 |
| current DMARD therapy Units: Subjects | | | |
| current DMARD therapy | 169 | 187 | 356 |
| no current DMARD therapy | 55 | 38 | 93 |
| RF/anti-CCP | | | |
| This system cannot create categories that are non-mutually exclusive. | | | |
| Units: Subjects | | | |
| both negative | 57 | 45 | 102 |
| RF pos/aCCP neg | 48 | 46 | 94 |
| RF neg/aCCP pos | 13 | 19 | 32 |
| both positive | 106 | 115 | 221 |

| | | | |
|--|---------|---------|---|
| BMI | | | |
| body mass index | | | |
| Units: kg/m ² | | | |
| arithmetic mean | 27.2 | 27.2 | |
| standard deviation | ± 4.5 | ± 4.4 | - |
| disease duration | | | |
| Units: years | | | |
| arithmetic mean | 10.8 | 10.4 | |
| standard deviation | ± 10.4 | ± 10.2 | - |
| DAS28 | | | |
| The reported data refer to the safety population (n=449) | | | |
| Units: score | | | |
| arithmetic mean | 4.43 | 4.60 | |
| standard deviation | ± 1.04 | ± 1.05 | - |
| joint damage score (Sharp van der Heijde)-mean | | | |
| Units: score | | | |
| arithmetic mean | 20.0 | 17.2 | |
| standard deviation | ± 34.6 | ± 33.4 | - |
| joint damage score (Sharp van der Heijde)-median-Q1Q3 | | | |
| Units: score | | | |
| median | 7 | 6 | |
| inter-quartile range (Q1-Q3) | 2 to 20 | 2 to 15 | - |

End points

End points reporting groups

| | |
|--|--------------------------------------|
| Reporting group title | Active |
| Reporting group description: 1 prednisolone 5 mg capsule / day | |
| Reporting group title | Placebo |
| Reporting group description: 1 placebo capsule per day | |
| Subject analysis set title | study duration-safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: In the safety analyses, all patients who took at least one dose of study medication are included. | |
| Subject analysis set title | study duration-efficacy-modified ITT |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: in the modified intention to treat analysis, all subjects from the safety population are included that returned for at least one follow up assessment | |

Primary: primary safety endpoint

| | |
|--|-------------------------|
| End point title | primary safety endpoint |
| End point description: The number of patients with at least one adverse event of special interest (AESI), determined in the safety population. AESI define as either serious adverse event (SAE), or one of the following: any AE (except loss of efficacy, worsening of disease) that leads to the definite cessation of trial medication; <ul style="list-style-type: none">• a cardiovascular event (myocardial infarction, cerebrovascular event, peripheral arterial vascular event)• newly occurring hypertension requiring drug treatment;• newly occurring diabetes mellitus requiring drug treatment;• symptomatic bone fracture requiring treatment;• infection requiring antibiotic treatment;• newly occurring cataract or glaucoma. | |
| End point type | Primary |
| End point timeframe: study duration | |

| End point values | Active | Placebo | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 224 | 225 | | |
| Units: patients | | | | |
| endpoint met (at least one AESI) | 134 | 111 | | |
| endpoint not met | 90 | 114 | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | primary harm outcome analysis |
| Comparison groups | Placebo v Active |
| Number of subjects included in analysis | 449 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 ^[1] |
| Method | GEE |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.24 |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| lower limit | 1.04 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.12 |

Notes:

[1] - one-sided.

Primary: mean DAS28 change post baseline

| | |
|--|---------------------------------|
| End point title | mean DAS28 change post baseline |
| End point description: | |
| Placebo group is reference. The negative sign of the treatment effect indicates that disease activity was lower in the prednisolone group. | |
| This system does not allow reporting of intermediate timepoints. See figure. | |
| The longitudinal model estimated the overall treatment effect on the change, adjusted for time point and stratification factors. | |
| The statistical analysis of change is given at 24 months. | |
| End point type | Primary |
| End point timeframe: | |
| Measured at month 3,6,12,18,24 (mITT population). | |

| End point values | Active | Placebo | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 221 | 223 | | |
| Units: score | | | | |
| arithmetic mean (standard error) | -0.37 (± 0.14) | 0 (± 0) | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Change in DAS28 over time (primary model)/Fig for Eudract.tiff |
|-----------------------------------|--|

Statistical analyses

| | |
|--|-----------------------------------|
| Statistical analysis title | primary efficacy analysis (DAS28) |
| Statistical analysis description: | |
| analysis performed on the mITT population. Negative sign indicates disease activity decreased more in prednisolone than in placebo patients. | |
| Comparison groups | Placebo v Active |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[2] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.37 |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| upper limit | -0.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.08 |

Notes:

[2] - one-sided.

Secondary: change in Sharp van der Heijde damage score

| | |
|--|---|
| End point title | change in Sharp van der Heijde damage score |
| End point description: | |
| Change expressed as score at end of trial minus score at baseline. | |
| End point type | Secondary |
| End point timeframe: | |
| study duration | |

| End point values | Active | Placebo | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 221 | 223 | | |
| Units: score | | | | |
| arithmetic mean (standard deviation) | 0.3 (± 1.0) | 1.9 (± 6.4) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | difference in damage progression |
| Comparison groups | Active v Placebo |
| Number of subjects included in analysis | 444 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.003 ^[4] |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.7 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| lower limit | 0.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.6 |

Notes:

[3] - The positive difference indicates that prednisolone patients had less damage progression than placebo.

[4] - there is no comment, but the system generates an error on this field.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing the ICF until month 27.

Adverse event reporting additional description:

AEs, AESIs and SAEs

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 21 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Prednisolone-Active |
|-----------------------|---------------------|

Reporting group description:

Active treatment group

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo group

| Serious adverse events | Prednisolone-Active | Placebo | |
|---|---------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 55 / 224 (24.55%) | 46 / 225 (20.44%) | |
| number of deaths (all causes) | 3 | 2 | |
| number of deaths resulting from adverse events | 3 | 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| neoplasms | | | |
| subjects affected / exposed | 9 / 224 (4.02%) | 7 / 225 (3.11%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| injuries | | | |
| subjects affected / exposed | 3 / 224 (1.34%) | 6 / 225 (2.67%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| cardiac disorders | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 5 / 224 (2.23%) | 8 / 225 (3.56%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Nervous system disorders | | | |
| nervous system disorders | | | |
| subjects affected / exposed | 6 / 224 (2.68%) | 7 / 225 (3.11%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| general disorders | | | |
| subjects affected / exposed | 15 / 224 (6.70%) | 10 / 225 (4.44%) | |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Eye disorder | | | |
| subjects affected / exposed | 0 / 224 (0.00%) | 1 / 225 (0.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 6 / 224 (2.68%) | 2 / 225 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| respiratory | | | |
| subjects affected / exposed | 7 / 224 (3.13%) | 3 / 225 (1.33%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| infections | | | |
| subjects affected / exposed | 22 / 224 (9.82%) | 12 / 225 (5.33%) | |
| occurrences causally related to treatment / all | 0 / 26 | 0 / 16 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

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

| Non-serious adverse events | Prednisolone-Active | Placebo | |
|---|--|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 173 / 224 (77.23%) | 167 / 225 (74.22%) | |
| Blood and lymphatic system disorders | | | |
| total nonserious events | Additional description: Nonserious events are not reported by SOC, this will be reported in the main scientific publication. However, this system does not accept that (ERROR messages preventing successful validation). Therefore, totals repeated here. | | |
| subjects affected / exposed | 173 / 224 (77.23%) | 167 / 225 (74.22%) | |
| occurrences (all) | 906 | 669 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 12 April 2019 | <ul style="list-style-type: none">- adjustment of eligibility criteria (lower disease activity, and less stringent requirements for stable conc antirheumatic therapy)- strongly reduced sample size based on blinded interim analysis of the incidence of the primary outcome for harm. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported