



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
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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
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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:	<p>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.</p>
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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21
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Reporting groups

Reporting group title	Prednisolone-Active
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Reporting group description:

Active treatment group

Reporting group title	Placebo
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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	- 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