Clinical trial results:
A randomised, double-blind, placebo-controlled proof-of concept study of the efficacy and safety of gevokizumab in the treatment of patients with giant cell arteritis

Summary

EudraCT number	2013-002778-38
Trial protocol	IT ES GB CZ FI DK BE AT IE EE
Global end of trial date	28 October 2015

Results information

Result version number	v1 (current)
This version publication date	04 December 2016
First version publication date	04 December 2016

Trial information

Trial identification

Sponsor protocol code	CL2-78989-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1144-7133

Notes:

Sponsors

Sponsor organisation name	Laboratorios Servier SL
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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	28 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2015
Global end of trial reached?	Yes
Global end of trial date	28 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the efficacy and safety of gevokizumab on symptoms of giant cell arteritis (GCA) in relapsing patients receiving systemic oral corticosteroids (CS)

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	22 August 2014
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	Norway: 3
Country: Number of subjects enrolled	United Kingdom: 1

Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Russian Federation: 5
Worldwide total number of subjects	13
EEA total number of subjects	7

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)	2
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were male or female of age 50 years, with GCA according to modified American College of Rheumatology criteria, with symptoms of relapse restricted to PolyMyalgia Rheumatica -like or systemic symptoms associated with elevated Erythrocyte Sedimentation Rate and/or C Reactive Protein and receiving oral CS (range: 5 - 30 mg/day).

Period 1

Period 1 title	Double-blind treatment period (W0-W24)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Gevokizumab 60mg

Arm description:

Gevokizumab 60mg [W0-W24]

Arm type	Experimental
Investigational medicinal product name	Gevokizumab
Investigational medicinal product code	S78989
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One subcutaneous administration of Gevokizumab every 4 weeks (i.e. Q4W) until W20, with a supplementary injection at W002, for a total of 7 doses in the first period of the study.

Arm title	Placebo

Arm description:

Placebo [W0-W24]

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One subcutaneous administration of Placebo every 4 weeks (i.e. Q4W) until W20, with a supplementary injection at W002, for a total of 7 doses in the first period of the study.

Number of subjects in period 1	Gevokizumab 60mg	Placebo
Started	6	7
Completed	2	5
Not completed	4	2
Adverse event, non-fatal	1	-
Study discontinuation	2	2
Protocol deviation	1	-

Period 2	
Period 2 title	Open label period (W24-W52)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Gevokizumab 60mg

Arm description:

Gevokizumab 60mg (W24-W52)

Arm type	Experimental
Investigational medicinal product name	Gevokizumab
Investigational medicinal product code	S78989
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

One subcutaneous injection of Gevokizumab 60 mg at each visit (except W052) for a maximum of 7 administrations.

Number of subjects in period 2	Gevokizumab 60mg
Started	7
Completed	1
Not completed	6
Adverse event, non-fatal	1
Study discontinuation	5

Baseline characteristics

Reporting groups	
Reporting group title	Gevokizumab 60mg
Reporting group description: Gevokizumab 60mg [W0-W24]	
Reporting group title	Placebo
Reporting group description: Placebo [W0-W24]	

Reporting group values	Gevokizumab 60mg	Placebo	Total
Number of subjects	6	7	13
Age categorical Units: Subjects			
Adults (18-64 years)	1	1	2
From 65-84 years	5	6	11
Age continuous Units: years			
arithmetic mean	71.7	71.6	
standard deviation	± 6.7	± 5.8	-
Gender categorical Units: Subjects			
Female	6	4	10
Male	0	3	3

End points

End points reporting groups

Reporting group title	Gevokizumab 60mg
Reporting group description: Gevokizumab 60mg [W0-W24]	
Reporting group title	Placebo
Reporting group description: Placebo [W0-W24]	
Reporting group title	Gevokizumab 60mg
Reporting group description: Gevokizumab 60mg (W24-W52)	

Primary: Response on a composite endpoint

End point title	Response on a composite endpoint[1]

End point description:

Response to treatment at the W004 visit:
- Normalisation or ≥ 70% decrease in ESR and/or CRP, and
- ≥70% improvement in PMR-like/systemic symptoms according to the PaGA using a VAS, and
- ≥70% improvement in morning stiffness duration and intensity (VAS), and
- No appearance of other GCA features, and
- No CS dose increase.

End point type	Primary

End point timeframe:

Response at W4

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: Only a descriptive analysis of the primary endpoint was specified (proportion of responders) in view of the small sample size (premature discontinuation of study).

End point values	Gevokizumab 60mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: Number of responders	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Over the double-blind treatment period (W0 - W24): all adverse events occurred, worsened or became serious between the first IMP intake date (included) during the double-blind treatment and the first IMP intake date during open-label period (excluded).

Adverse event reporting additional description:

Over the open-label period: All adverse events occurring after W24 (included)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Gevokizumab 60mg [W0-W24]
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Gevokizumab 60mg [W24-W52]

Reporting group description: -

Serious adverse events	Gevokizumab 60mg [W0-W24]	Placebo	Gevokizumab 60mg [W24-W52]
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	2 / 7 (28.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Radiotherapy to brain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Insulin-requiring type 2 diabetes mellitus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 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: 5 %

Non-serious adverse events	Gevokizumab 60mg [W0-W24]	Placebo	Gevokizumab 60mg [W24-W52]
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 6 (83.33%)	6 / 7 (85.71%)	5 / 7 (71.43%)
Vascular disorders			
Temporal arteritis			
subjects affected / exposed	1 / 6 (16.67%)	2 / 7 (28.57%)	2 / 7 (28.57%)
occurrences (all)	1	2	2
Hypertension			

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dyspnoea paroxysmal nocturnal			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Investigations			
Blood pressure systolic increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Eye symptom			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Trigeminal neuralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Eye disorders			
Cataract			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Inguinal hernia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gastroduodenitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Leukocyturia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Spinal osteoarthritis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bacteriuria			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Infective exacerbation of chronic obstructive airways disease			

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Streptococcal urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2013	Applicable in all countries. 2 main objectives: - The inclusion of patients whose diagnosis of Giant Cell Arteritis (GCA) had been confirmed by high-resolution colour Doppler Ultrasound (US). - An alternative CS tapering schedule in case of non-availability of the 1 mg prednisone dose in some countries.
01 October 2014	Applicable in all countries. Mainly aimed at modifying the medical and therapeutic eligibility criteria, authorizing the selection of the following patient profiles: - Patients experiencing their first GCA relapse. - Patients on continuous CS treatment for more than 2 years. - Patients with a positive imaging confirming the GCA diagnosis performed more than 12 weeks before inclusion in case of absent or negative biopsy at the time of diagnosis.
23 December 2014	Applicable in all countries. The main changes were: - Authorised the selection of patients with an increase in CS dose to treat the current relapse if the increase occurred more than one month before selection and the dosage was stable since then. - Modified the ACR criteria: * Replacement of "ESR >=50 mm/hour" by "ESR >= 50 mm/hour and/or CRP >= 2.5 mg/dL (i.e. 25 mg/L)". * Inclusion of the imaging exam, which was already an eligibility criterion in case of absent or negative temporal biopsy, within the ACR criteria. - Suppressed the non-selection criterion "patients with a history of chronic inflammatory disease". - Added chronic immunosuppressants for indications other than GCA as forbidden concomitant treatments.
11 August 2015	Applicable in all countries. This amendment added a new dose (120 mg) of gevokizumab to be tested in the study for newly-included patients. No patients were included after its approval; the higher dose was not therefore used in the study. Amendment 5 also specified that the 5th criterion of the modified ACR classification for GCA diagnosis (positive biopsy or imaging) was mandatory for patient inclusion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 September 2015	The Sponsor took the decision to prematurely discontinue the study for strategic reasons that were unrelated to any safety issue.	-

Notes:

Limitations and caveats

None reported