Clinical trial results:
A randomized, double-masked, placebo-controlled study of the efficacy of gevokizumab in the treatment of patients with Behçet's Disease uveitis
EYEGUARD TM -B

Summary

EudraCT number	2012-001125-27
Trial protocol	GB DE GR PT IT ES
Global end of trial date	29 September 2015

Results information

Result version number	v1 (current)
This version publication date	18 September 2016
First version publication date	18 September 2016

Trial information

Trial identification

Sponsor protocol code	CL3-78989-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01965145
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France,
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com

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 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 September 2015
Global end of trial reached?	Yes
Global end of trial date	29 September 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 demonstrate the superiority of gevokizumab as compared to placebo on top of current standard of care in reducing the risk of Behçet's disease uveitis exacerbations

Protection of trial subjects:

The 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:

Standard of care including oral corticosteroids and immunosuppressive therapy (azathioprine, mycophenolate mofetil / mycophenolate sodium,
cyclosporine-A and/or methotrexate alone or in any combination)

Evidence for comparator: -

Actual start date of recruitment	14 November 2012
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: 6
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Armenia: 6
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Korea, Republic of: 21
Country: Number of subjects enrolled	Tunisia: 1
Country: Number of subjects enrolled	Turkey: 24
Worldwide total number of subjects	84
EEA total number of subjects	24

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)	83
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients with a history of Behçet's disease with ocular involvement of the posterior segment, and having experienced at least 2 ocular exacerbations within the 18 months prior to selection, with the most recent having occurred within the last 4 months and having been treated successfully with high dose corticosteroids

Period 1

Period 1 title	Part 1 (overall period)
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

Arm description: -

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

Dosage and administration details:

- Subcutaneous dose of 60 mg gevokizumab beginning on Day 0 and administered every 4 weeks

Arm title	Placebo

Arm description: -

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:

-Subcutaneous dose of placebo beginning on Day 0 and administered every 4 weeks

Number of subjects in period 1	Gevokizumab	Placebo
Started	41	43
Completed	0	0
Not completed	41	43
non-medical reason	6	4
Adverse event, non-fatal	1	3

study discontinuation	34	34
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Gevokizumab
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Gevokizumab	Placebo	Total
Number of subjects	41	43	84
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)	41	42	83
From 65-84 years	0	1	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34.3	35.1	
standard deviation	± 9.6	± 9.5	-
Gender categorical Units: Subjects			
Female	12	12	24
Male	29	31	60

End points

End points reporting groups

Reporting group title	Gevokizumab
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Time to first acute ocular exacerbation over the Core study period

End point title	Time to first acute ocular exacerbation over the Core study period
End point description:	
End point type	Primary
End point timeframe:	
Duration of the core study period (event-driven), i.e. until the occurence of the 29th ocular exacerbation	

End point values	Gevokizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	43		
Units: number of pts with a 1st exacerbation	14	15		

Statistical analyses

Statistical analysis title	Cox's proportional hazard model adjusted
Comparison groups	Placebo v Gevokizumab
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.661
Method	Cox model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.77

Adverse events

Adverse events information

Timeframe for reporting adverse events:

EAEs reported during the Part 1 (i.e. the core study and the double masked extension period)

Adverse event reporting additional description:

Emergent adverse events are presented (EAEs) . EAEs on treatment were defined as all adverse events which occurred between the first injection date (included) and the last study drug injection date + 25 days (included), or which worsened or became serious.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Gevokizumab

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Gevokizumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 41 (31.71%)	14 / 43 (32.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Behcet's syndrome			
subjects affected / exposed	5 / 41 (12.20%)	5 / 43 (11.63%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			

subjects affected / exposed	0 / 41 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular ischaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular oedema			
subjects affected / exposed	0 / 41 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitic glaucoma			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	2 / 41 (4.88%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal ulcer haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			

subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep disorder			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Gevokizumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 41 (90.24%)	40 / 43 (93.02%)	
Investigations			
Blood triglycerides increased			
subjects affected / exposed	1 / 41 (2.44%)	3 / 43 (6.98%)	
occurrences (all)	1	4	
C-reactive protein increased			
subjects affected / exposed	2 / 41 (4.88%)	3 / 43 (6.98%)	
occurrences (all)	2	4	
Intraocular pressure increased			
subjects affected / exposed	5 / 41 (12.20%)	4 / 43 (9.30%)	
occurrences (all)	9	6	
Mycobacterium tuberculosis complex test positive			
subjects affected / exposed	2 / 41 (4.88%)	3 / 43 (6.98%)	
occurrences (all)	2	3	
Vascular disorders			
Behcet's syndrome			
subjects affected / exposed	23 / 41 (56.10%)	25 / 43 (58.14%)	
occurrences (all)	56	67	
Hypertension			
subjects affected / exposed	3 / 41 (7.32%)	2 / 43 (4.65%)	
occurrences (all)	3	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 41 (7.32%)	2 / 43 (4.65%)	
occurrences (all)	3	3	
Headache			
subjects affected / exposed	8 / 41 (19.51%)	6 / 43 (13.95%)	
occurrences (all)	13	7	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 41 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	

Fatigue			
subjects affected / exposed	0 / 41 (0.00%)	6 / 43 (13.95%)	
occurrences (all)	0	16	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 41 (4.88%)	6 / 43 (13.95%)	
occurrences (all)	2	8	
Eye pain			
subjects affected / exposed	3 / 41 (7.32%)	3 / 43 (6.98%)	
occurrences (all)	4	3	
Macular oedema			
subjects affected / exposed	4 / 41 (9.76%)	14 / 43 (32.56%)	
occurrences (all)	11	33	
Vision blurred			
subjects affected / exposed	5 / 41 (12.20%)	0 / 43 (0.00%)	
occurrences (all)	11	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 41 (9.76%)	1 / 43 (2.33%)	
occurrences (all)	4	1	
Abdominal pain upper			
subjects affected / exposed	3 / 41 (7.32%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	1 / 41 (2.44%)	3 / 43 (6.98%)	
occurrences (all)	1	3	
Diarrhoea			
subjects affected / exposed	4 / 41 (9.76%)	4 / 43 (9.30%)	
occurrences (all)	5	5	
Nausea			
subjects affected / exposed	4 / 41 (9.76%)	3 / 43 (6.98%)	
occurrences (all)	5	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 41 (2.44%)	3 / 43 (6.98%)	
occurrences (all)	1	3	

Skin and subcutaneous tissue disorders			
Swelling face			
subjects affected / exposed	0 / 41 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 41 (12.20%)	2 / 43 (4.65%)	
occurrences (all)	5	2	
Back pain			
subjects affected / exposed	0 / 41 (0.00%)	4 / 43 (9.30%)	
occurrences (all)	0	4	
Myalgia			
subjects affected / exposed	3 / 41 (7.32%)	3 / 43 (6.98%)	
occurrences (all)	5	3	
Pain in extremity			
subjects affected / exposed	3 / 41 (7.32%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 41 (2.44%)	3 / 43 (6.98%)	
occurrences (all)	1	3	
Nasopharyngitis			
subjects affected / exposed	6 / 41 (14.63%)	6 / 43 (13.95%)	
occurrences (all)	7	7	
Upper respiratory tract infection			
subjects affected / exposed	4 / 41 (9.76%)	3 / 43 (6.98%)	
occurrences (all)	6	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2012	– Precision in contraception methods; – Introduction of 6 months wash out period for subtenonian triamcinolone acetonide; – Introduction of macular oedema as a rescue criterion; – Introduction of OCT at each visit with ophthalmologic exam – Additional tests for HIV, HCV, hepatitis B and IGRA
07 November 2013	-- Increase the statistical power from 80% to 90% while maintaining the same hazard ratio and type one error rate planned in the protocol for the determination of the number of events. -- Eliminate the upper weight limit of 120 kg in the selection criteria. -- Extend the delay between selection (ASSE) and inclusion (D0) from 7 to 10 days.
28 January 2015	-- Update of the study completion date. -- Postponment of immune competence assessment - Cessation of laboratory sampling for cytokines, vascular markers, genomics / other omics after the end of the Core study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 July 2015	At the end of the Core study period, the study discontinuation was decided owing to Sponsor's decision, (primary endpoint not achieved). Consequently the 1-year double masked extension period had been prematurely stopped and the open long-term safety follow-up period was not carried on.	-

Notes:

Limitations and caveats

None reported