Clinical trial results:
Dose-response study of gevokizumab (S78989) 3mg, 10mg, 30mg or 60mg in patients with type 2 diabetes and diabetic kidney disease (DKD). A 66-week, international, multicenter, randomized, double-blind, parallel-group, placebo controlled study.

Summary

EudraCT number	2013-003610-41
Trial protocol	CZ SK BE DE DK SE ES PT PL
Global end of trial date	28 October 2015

Results information

Result version number	v1 (current)
This version publication date	27 August 2016
First version publication date	27 August 2016

Trial information

Trial identification

Sponsor protocol code	CL2-78989-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1146-9287

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1 55 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	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 primary objective of the study was to detect the existence of an overall dose-response relationship with gevokizumab (3 mg, 10 mg, 30 mg, or 60 mg) subcutaneous (SC), on the measured glomerular filtration rate (mGFR) in patients with type 2 diabetes and diabetic kidney disease (DKD) using the rate of decline of kidney function, assessed by the glomerular filtration rate measured (mGFR) by plasma clearance of iohexol after 52 weeks of treatment.

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:

Patients were to be treated with:
- an angiotensin converting enzyme (ACE) inhibitor or by angiotensin-II receptor blocker (ARB) unless medically justified and documented
- at least one glucose-lowering therapy (insulin included) (Dapagliflozin or any SGLT 2 inhibitors were prohibited).

Evidence for comparator: -

Actual start date of recruitment	24 April 2015
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	Australia: 1
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Korea, Republic of: 6
Worldwide total number of subjects	14
EEA total number of subjects	2

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)	6
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male or female ≤ 85 years old with diagnosis of type 2 diabetes mellitus first made at age ≥ 30 years, ≥ 8 years prior to selection, Estimated glomerular filtration rate (eGFR) within 20-60 mL/min/1.73 m² range and Urinary albumin/creatinine ratio (UACR)> 300 mg/g. HbA1c <10% with at least one glucose-lowering therapy (insulin incl.) at stable dose

Period 1

Period 1 title	treatment period (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 3mg

Arm description: -

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 3 mg at inclusion and every 4 weeks until W48

Arm title	Gevokizumab 10mg

Arm description: -

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 10 mg at inclusion and every 4 weeks until W48

Arm title	Gevokizumab 30mg

Arm description: -

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 30 mg at inclusion and every 4 weeks until W48

Arm title	Gevokizumab 60mg

Arm description: -	
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 inclusion and every 4 weeks until W48

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:

one subcutaneous injection of placebo at inclusion and every 4 weeks until W48

Number of subjects in period 1	Gevokizumab 3mg	Gevokizumab 10mg	Gevokizumab 30mg
Started	3	3	2
Completed	0	0	0
Not completed	3	3	2
Sponsor’s decision to discontinue the study	3	3	2

Number of subjects in period 1	Gevokizumab 60mg	Placebo
Started	3	3
Completed	0	0
Not completed	3	3
Sponsor’s decision to discontinue the study	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Gevokizumab 3mg
Reporting group description: -	
Reporting group title	Gevokizumab 10mg
Reporting group description: -	
Reporting group title	Gevokizumab 30mg
Reporting group description: -	
Reporting group title	Gevokizumab 60mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Gevokizumab 3mg	Gevokizumab 10mg	Gevokizumab 30mg
Number of subjects	3	3	2
Age categorical Units: Subjects			
Adults (18-64 years)	2	0	1
From 65-84 years	1	3	1
Gender categorical Units: Subjects			
Female	0	1	0
Male	3	2	2

Reporting group values	Gevokizumab 60mg	Placebo	Total
Number of subjects	3	3	14
Age categorical Units: Subjects			
Adults (18-64 years)	1	2	6
From 65-84 years	2	1	8
Gender categorical Units: Subjects			
Female	0	1	2
Male	3	2	12

End points

End points reporting groups

Reporting group title	Gevokizumab 3mg
Reporting group description: -	
Reporting group title	Gevokizumab 10mg
Reporting group description: -	
Reporting group title	Gevokizumab 30mg
Reporting group description: -	
Reporting group title	Gevokizumab 60mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Included Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients included and having at least one dose of IMP.

Primary: Change from baseline to W52 in mGFR

End point title	Change from baseline to W52 in mGFR[1]

End point description:

The primary endpoint was the mGFR measured by plasma clearance of an exogenous filtration marker

End point type	Primary

End point timeframe:

At W0, W24, and W52 visit (end of study visit) or premature discontinuation visit

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: In the specific context of the study (study discontinued due to general strategic and business reasons unrelated to safety), it was decided to not perform the efficacy analyses planned in the study protocol. No mGFR data available under treatment.

End point values	Included Set			
Subject group type	Subject analysis set			
Number of subjects analysed	0[2]			
Units: mL/min/1.73 m²				
arithmetic mean (standard deviation)	()			

Notes:

[2] - No primary endpoint analysed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events which occurred, worsened, or became serious according to the investigator or upgraded by the Sponsor, after the first IMP intake date (included).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Gevokizumab 3mg
Reporting group description: -	
Reporting group title	Gevokizumab 10mg
Reporting group description: -	
Reporting group title	Gevokizumab 30mg
Reporting group description: -	
Reporting group title	Gevokizumab 60mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Gevokizumab 3mg	Gevokizumab 10mg	Gevokizumab 30mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (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
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (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

Serious adverse events	Gevokizumab 60mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	

number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Gevokizumab 3mg	Gevokizumab 10mg	Gevokizumab 30mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	1 / 2 (50.00%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Serum ferritin decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Animal scratch			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
General disorders and administration			

site conditions			
Injection site pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Vessel puncture site haemorrhage			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Injection site pruritus			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	1 / 2 (50.00%)
occurrences (all)	0	2	2
Umbilical hernia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Onychoclasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Gevokizumab 60mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Serum ferritin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Animal scratch			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Contusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Vessel puncture site haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Malaise			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Injection site pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Umbilical hernia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Onychoclasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2015	Concerned all centres in all countries. Main changes were the following: - Modification of Diet in renal Disease (MDRD) equation noted in the protocol was replaced. - Modification of total amount of blood volume withdrawn over the study (maximum blood volume to be sampled per visit: initially 65 mL brought to 89 mL). - Urinary Albumin/Creatinine Ratio (UACR) conversion factor was updated: 300 mg/g was to be equivalent to 34 mg/mmol, instead of 30 mg/mmol. - Regarding incl/sel criterion and allowed prior/concomitant medications, the Amendment clarified that anti-hyperglycemic medication taken by patients should be at a stable dose for at least 6 weeks prior to selection visit. - The protocol mentionned that ophthalmological examination assessed by fundal examination was to be performed by an ophthalmologist. Following this Amendment it was not required that fundal examinations are to be performed by ophthalmologists only. - At selection (ASS2) visit, new or worsened clinically significant abnormalities noticed during the physical examination should be reported in Medical History instead of being reported as adverse events. - A Section related to "Dialysis during the course of the study" was added in the study protocol for patients suffering from acute kidney injury (AKI) and for patients reaching end-stage renal disease (ESRD) suffering from progressive GFR decline. In addtion, the premature discontinuation criteria were updated accordingly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 September 2015	The study was prematurely discontinued due to a strategic decision unrelated to the safety	-

Notes:

Limitations and caveats

None reported