Document title	**CLINICAL STUDY REPORT SYNOPSIS** **Dose-response study of gevokizumab (S 78989) 3mg, 10mg, 30mg or 60mg in patients with type 2 diabetes and diabetic kidney disease (DKD)** **A 66-week, international, multicentre, randomised, double-blind, parallel-group, placebo controlled study**
Test drug code	**S 78989** (Gevokizumab)
Indication	Diabetic kidney disease in patients with type 2 diabetes
Development phase	Phase IIb
Protocol code	CL2-78989-011
Study initiation date	24 April 2015
Study completion date	28 October 2015
Main coordinator	[redacted]
Sponsor(s)	**Institut de Recherches Internationales Servier (I.R.I.S.)** 50 rue Carnot, 92284 Suresnes Cedex, FRANCE **Laboratorios Servier S.L.** Avenida de los Madroños 33, 28043 Madrid, SPAIN **Servier Canada Inc.** 235 Armand-Frappier Blvd, Laval, Quebec, H7V 4A7 CANADA
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	14 June 2016
Version of the report	Final version
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Gevokizumab (S 78989)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Dose-response study of gevokizumab (S 78989) 3 mg, 10 mg, 30 mg or 60 mg in patients with type 2 diabetes and diabetic kidney disease (DKD).
A 66-week, international, multicentre, randomised, double-blind, placebo-controlled phase IIb study.

Protocol No.: CL2-78989-011
EudraCT No.: 2013-003610-41
The description of the study protocol given hereafter includes the modifications of the 6 substantial amendments to the protocol.

International coordinator: [redacted]

Study centres:
In all, 11 centres located in 5 countries included a total of 14 patients: 1 centre in Australia (1 patient included), 2 centres in Canada (3 patients included), 2 centres in Czech Republic (2 patients included), 2 centres in South Africa (2 patients included) and 4 centres in South Korea (6 patients included).

Publication (reference): Not Applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 24 April 2015 (date of first visit first patient) Completion date: 28 October 2015 (date of last visit last patient)	phase IIb

Objectives:
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.

The **secondary objectives** of the study were:
- To determine a dose window for the Minimal Effective Dose (MED) for a 30% reduction in decline of GFR relative to placebo.
- To identify the best creatinine and/or cystatin C-based equation to estimate GFR in patients with DKD treated with gevokizumab.
- To explore the effect of gevokizumab on albuminuria and on a panel of serum and urinary concentrations of biomarkers of renal damage, inflammation, cardiovascular risk and bone mineral metabolism.
- To assess the safety profile of gevokizumab of each tested dose of gevokizumab in the study population.
- To assess pharmacokinetics of gevokizumab after repeated administration in the study population.

Methodology:
This was a phase IIb, multicentre, multinational randomized, parallel group, placebo-controlled, double-blind, dose-ranging study conducted in patients with type 2 diabetes mellitus and diabetic kidney disease (DKD).
At inclusion, patients were randomized through an Interactive Web Response System (IWRS) either to placebo or to one of the four different dosages of gevokizumab (3 mg, 10 mg, 30 mg or 60 mg), with stratification on eGFR (patients above/below 45 mL/min/1.73 m²), and geographic regions. The test drug or placebo was administered subcutaneously every four weeks (Q4W) from W0 to W48 for a total of 13 drug administrations.

This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

As the study was prematurely discontinued due to general strategic and business reasons unrelated to safety, an abbreviated report was written.

Number of patients:
Planned: 370 patients: 74 patients per S 78989 group (3 mg, 10 mg, 30 mg and 60 mg) and 74 patients in the placebo group.
Included: 14 patients: 3 in the S 78989 3 mg, 3 in the S 78989 10 mg, 2 in the S 78989 30 mg, 3 in the S 78989 60 mg, and 3 in the placebo group.
The number of patients included was much lower than planned due to study discontinuation.

Diagnosis and main criteria for inclusion:
Male or female patients ≤ 85 years old (except for countries with local regulation), with a diagnosis of type 2 diabetes mellitus first made at age ≥ 30 years and ≥ 8 years prior to selection and an estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) equation, within the 20-60 mL/min/1.73 m² range (inclusive), and urinary albumin-to-creatinine ratio (UACR)> 300 mg/g. Patients were to be on angiotensin converting enzyme (ACE) inhibitor or angiotensin-II receptor blocker (ARB) unless medically justified.
In addition, diabetic retinopathy confirmed by ophthalmological assessment for Belgium, Denmark, Germany, Portugal, Romania, Spain and Sweden, as added by Amendment No. 1 and HbA1c <10%, with at least one glucose-lowering therapy (insulin included) for at least six months prior to selection, and as added Amendment No. 5 at stable dose for at least 6 months prior to selection visit (Dapagliflozin or any SGLT 2 inhibitors were prohibited).

Test drug:
S 78989 (gevokizumab): one subcutaneous injection of either 3 mg, 10 mg, 30 mg or 60 mg at inclusion and every 4 weeks until W48). Batch No.: Gevokizumab 3 mg: L0057420; 10 mg: L0055032; 30 mg: L0055034; 60mg: L0055035

Comparator (Reference product and/or placebo):
Matching placebo: one subcutaneous injection at inclusion and every 4 weeks until W48.

Batch No. for the filtration marker Iohexol: L0057512.

Duration of treatment:
Run-in period: 6 weeks without Investigational Medicinal Products (IMP) (from ASS1 to W0).
Treatment period: 52 weeks (one SC injection every 4 weeks from W0 to W48).
Follow-up period: 18 weeks after the last SC injection of the IMP *i.e.* W66**.**

Criteria for evaluation:

Efficacy measurements:

Primary efficacy endpoint:

- GFR measured by plasma clearance of an exogenous filtration marker (non-radioactive iohexol) at W0, W24, and W52 visit (end of study visit) or premature discontinuation visit (data not transferred)

Secondary efficacy endpoints:

- Estimated GFR (eGFR) calculated with endogenous filtration marker equations based serum creatinine (MDRD) and/or serum cystatin C (CKD-EPI).
- Albuminuria, estimated by the albumin to creatinine ratio (UACR) on triplicate first morning void urine samples.
- Number of patients with 15% reduction in eGFR per year.

Secondary efficacy endpoints were to be performed at ASS2, W0, W4, W12, W20, W24, W36, W48, W52 (or premature discontinuation visit when possible) and W66 visit.

To note: due to the specific context of the study statistical analyses for efficacy endpoints were not performed.

Safety measurements:

The clinical safety measurements concerned the effects of each dose of gevokizumab *versus* placebo on :

- Adverse events, assessed at each visit.
- Laboratory parameters (haematology panel, biochemistry panel, and urinalysis), assessed by central laboratory at visits ASS2, W0, W4, W12, W24, W36, W48, W52 (or premature discontinuation visit when possible) and W66 visit. HbA1c (performed at ASS2, W0, W12, W24, W36, W52, W66 and premature discontinuation when possible).
- TSH (performed at ASS2; additional dosage was to be performed at W20 and W48 visits for Belgium, Denmark, Germany, Portugal, Romania, Spain, and Sweden, as added by Amendment No. 1)
- IGRA test performed at ASS2 (and at W52 or end of study or premature discontinuation for South Korea only, as added by Amendment No. 4).
- Vital signs including blood pressure (systolic/ diastolic), pulse rate, weight and body temperature, assessed at each visit, and height measured at ASS2 visit only.
- Standard 12-lead Electrocardiogram (ECG), performed at ASS2 visit and at W52 (end of study) visit (or premature discontinuation visit when possible).
- Ophthalmological assessment (fundal examination), performed at W0 and at W52 visit (or premature discontinuation visit when possible).
- Chest X-ray at W0 for patients without any chest X-ray done within the 12 weeks prior to selection, and at W52 (end of study or premature discontinuation) for South Korea only, as added by Amendment No. 4.

Other measurements not specifically related to efficacy or safety:

Pharmacokinetics (PK) and Anti-Drug Antibodies (ADA):

Initially gevokizumab concentration-time data were to be analysed by population pharmacokinetics approach but due to the context of the study (study discontinuation), neither PK nor ADA analysis was performed.

Other assessments:

- A panel of exploratory biomarkers of renal damage, inflammation, cardiovascular risk and bone mineral metabolism.
- Pharmacogenomics (genomic biomarkers) was optional for the patients (required a specific consent).

To note: due to the context of the study, exploratory biomarkers, and pharmacogenomics assessments were not analysed (samples were not assayed).

Statistical methods:

Analysis Set:

All statistical analyses were performed only on the Included Set, as there was no difference between the Included Set, the Randomised Set and the Safety Set.

Efficacy analysis:

Due to the context of the study (study discontinuation), no statistical analysis of efficacy endpoints was performed. Primary endpoint was not described as data were not transferred; secondary efficacy endpoints were described using individual data listings on the IS.

Study outcome and safety analysis: Descriptive statistics (and individual listings) were provided in the IS.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Due to a decision made by the Sponsor for general strategic and business reasons unrelated to safety, this study was prematurely discontinued and results are described in this abbreviated study report.

Status	Gevokizumab				Placebo	All
	3 mg	10 mg	30 mg	60 mg		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Included	3	3	2	3	3	14
Withdrawn due to						
non-medical reason	3 (100)	3 (100)	2 (100)	3 (100)	3 (100)	14 (100)
Completed	-	-	-	-	-	-
Randomised Set	3 (100)	3 (100)	2 (100)	3 (100)	3 (100)	14 (100)
Safety set	3 (100)	3 (100)	2 (100)	3 (100)	3 (100)	14 (100)

n: number of patients
%: % of the Included Set

The 14 included patients had a total of 33 protocol deviations before or at inclusion. These deviations concerned mostly selection/inclusion criteria not fulfilled (28 deviations, in all patients), mainly UACR $\leq$ 300 mg/g at ASS2 visit (12 deviations in 12 patients). No protocol deviation was reported after inclusion.

BASELINE CHARACTERISTICS

It is noteworthy that all the results presented in this abbreviated report should be interpreted cautiously due to the small number of patients in each group (N = 2 or 3 patients).

At inclusion, among the 14 included patients, 6 were aged from 18 to 64 years, 8 were aged from 65 to 84 years and most of them (12/14) were male.
At selection, the duration of type 2 diabetes since diagnosis for patients having data available (4/14 patients) ranged between 188 and 200 months (approximately 15 and 17 years respectively) and the duration of diabetic kidney disease since diagnosis (for the 10/14 patients with available data) was comprised between 12 and 158 months (*i.e.,* respectively one year and 13 years). In addition, 8/14 patients had diabetic retinopathy at selection.
In the Included Set, eGFR ranged between 18 and 58 mL/min/1.73m^2 and UACR between 35 and 2912 mg/g.

EXTENT OF EXPOSURE

Overall, the treatment duration was shorter than planned due to the study discontinuation and ranged between 28 and 161 days with a mean ± SD of 64.5 ± 37.4 days (median of 55.5 days).

EFFICACY RESULTS

In the specific context of the study, it was decided to not perform the efficacy analyses planned in the protocol.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

- **Emergent adverse events**

Overall summary for adverse events in the Included Set

		Gevokizumab				
		3 mg (N = 3)	**10 mg (N = 3)**	**30 mg (N = 2)**	**60 mg (N = 3)**	**Placebo (N = 3)**
Patients having reported						
at least one EAE	n (%)	1 (33.3)	2 (66.7)	1(50.0)	2 (66.7)	1 (33.3)
at least one treatment-related EAE	n (%)	1 (33.3)	-	1 (50.0)	-	-
Patients having experienced		-	-	-	-	-
at least one serious AE (including death)	n (%)	-	1 (33.3)	-	-	-
at least one serious EAE (including death)	n(%)		1 (33.3)			
at least one treatment-related serious AE	n (%)	-	-	-	-	-
Patients with treatment withdrawal	n (%)	-	-	-	-	-
Patients who died	n (%)	-	-	-	-	-

N: number of patients by treatment group; n: number of patients

No **death** occurred in this study and no patient experienced an EAE that led to study **drug withdrawal**.
In all, 7/14 patients reported a total of 24 **EAEs on treatment** which were all reported once in each treatment group, except diarrhoea reported by 2 patients in the gevokizumab 10 mg group). Most of these EAEs (22/24 EAEs) were rated mild or moderate, while 2 EAEs (in one patient) were rated **severe** (anaemia, chronic kidney disease) and resolved.
A total of 6 EAEs considered to be **related to the study drug** according to investigator's opinion were reported in 2 patients (injection site pain and injection site pruritus in one patient in the 3 mg group, and diarrhoea [2 events], onychoclasis and malaise in one patient in the 30 mg group). All of these events were of mild intensity, non-serious and resolved/were resolving.
One EAE in the 3 mg group was reported as **not resolved** according to last information available. This event, umbilical hernia, was of mild intensity, non-serious, and considered as not related to the study drug/protocol.
In all, 5/14 patients experienced a total of 6 EAEs of **specific interest**: 2 events related to anaphylactic reaction/hypersensitivity (injection site pruritus, urticaria) and 4 events related to infection (one urinary tract infection and 3 nasopharyngitis). Of them, one was considered as related to the study drug according to the investigator (injection site pruritus). None were judged serious.
In all, 2 **serious** EAEs (chronic kidney disease, anaemia) were reported in one patient in the 10 mg group. These serious events were considered as not related to the study drug by the investigator and the patient recovered.

- **Laboratory tests**

Biochemical and haematological emergent PCSA values under treatment were sparse in all treatment groups. Of note 3 emergent high PCSA glucose values reported in the gevokizumab 60 mg group.

- **Other safety evaluation**

No relevant change through the study was observed regarding vital signs and clinical examination.
In all, 5/14 patients had a positive **TB-Test** at ASS2, including one patient who became negative at W8 visit. All these positive patients received prophylactic anti-tuberculosis treatment during the study, as required in the study protocol. Regarding **chest-X rays**, no abnormality was reported in any patient at baseline or during the study.

CONCLUSION

This multinational, double-blind, placebo-controlled, dose-ranging phase IIb study was conducted in 14 patients with type 2 diabetes (T2D) and diabetic kidney disease (DKD), instead of the 370 initially planned. The Sponsor decided to discontinue the study for general strategic and business reasons not related to safety.
Due to the small number of patients included in each treatment group (N = 2 or 3), no statistical analysis was performed on efficacy endpoints, and no comparison between dose groups could be done. No safety concern was raised over the study period.

Date of the report: 14 June 2016

Version of the report: Final version