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| *Document title* | **ABBREVIATED CLINICAL STUDY REPORT SYNOPSIS** |
| *Study title* | **A safEtY opEn-label study of GevokizUmAb in the tReatment of patients with chronic non-infectious Uveitis Disease, an eXtension study**<br>**The EYEGUARD™-X study** |
| *Test drug code* | **S78989 (Gevokizumab)** |
| *Indication* | **Chronic non-infectious uveitis** |
| *Development phase* | **Phase III** |
| *Protocol code* | **CL3-78989-019** |
| *Study initiation date* | **14 August 2014** |
| *Study completion date* | **2 November 2015** |
| *Sponsors* | **Institut de Recherches Internationales Servier (I.R.I.S.)**<br>**50 rue Carnot**<br>**92284 Suresnes Cedex – France**<br>**Servier Canada Inc.**<br>**235, Bd Armand-Frappier**<br>**LAVAL (Québec) H7V4A7**<br>**Laboratorios Servier, S.L.**<br>**Departamento de Investigacion y Desarrollo**<br>**Avenida de los Madronos, 33**<br>**28043 Madrid – Spain**<br>**Les Laboratoires Servier Representative Office**<br>**Paveletskaya Sq, 2-3**<br>**115054 Moscow – Russia**<br>**Servier Research and Development ICTR**<br>**Wexham Springs, Framewood Road**<br>**Wexham Slough SL3 6RJ - UK** |
| *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* | **09 June 2016** |
| *Version of the report* | **Final version** |
| | ~~**CONFIDENTIAL**~~ |

## 2. SYNOPSIS

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| **Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France** | | *(For National Authority Use only)* |
| **Test drug**<br>**Name of Finished Product:**<br>**Name of Active Ingredient:**<br>Gevokizumab S78989 | | |
| **Individual Study Table Referring to Part of the Dossier** | **Volume:** | **Page:** |

**Title of study:** A saf*E*t*Y* op*E*n-label study of *G*evokiz*U*m*A*b in the t*R*eatment of patients with chronic non-infectious Uveitis *D*isease, an e*X*tension study.
The EYEGUARD™-X study.

Protocol No.: CL3-78989-019
EudraCT No.: 2013-004973-29
The description of the study protocol given hereafter includes the modifications of the 3 substantial amendments to the protocol.

**International Coordinator:** [redacted]

**Study centres:**
In all, 29 centres located in 12 countries included 77 patients: Australia (2 centres, 3 patients), Austria (2 centres, 4 patients), France (3 centres, 3 patients), Germany (4 centres, 6 patients), Greece (1 centre, 3 patients), Italy (2 centres, 4 patients), Republic of Korea (3 centres, 18 patients), Portugal (1 centre, 1 patient), Spain (3 centres, 10 patients), Taiwan (3 centres, 15 patients), Tunisia (1 centre, 2 patients), Turkey (4 centres, 8 patients).

**Publication (reference):** Not Applicable

| **Studied period:** | **Phase of development of the study:** |
|---|---|
| Initiation date: 14 August 2014<br>Completion date: 2 November 2015 - Study discontinuation of the trial (Sponsor's decision unrelated to safety) | phase III |

**Objectives:**
The primary objective of this study was to evaluate long-term safety of gevokizumab in patient with chronic non-infectious uveitis who previously well tolerated the study drug and may benefit from long-term treatment with gevokizumab.

**Methodology:**
This was an international, multicentre, open-label extension study providing continued dosing of gevokizumab in the treatment of subjects with chronic non-infectious uveitis. This study was conducted in non US patients who completed CL3-78989-002 (EYEGUARD™-B), X052130/CL3-78989-005 (EYEGUARD™-A) or X052131/CL3-78989-006 (EYEGUARD™-C) studies, or were receiving a gevokizumab treatment as compassionate use, and who met all eligibility criteria at Week 0.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

The study was prematurely discontinued following a Sponsor's decision unrelated to safety (primary endpoint not achieved in EYEGUARD B). At that time, 77 patients were included and none had completed the study.

**Number of patients:**
Planned: No more than 300 patients.
Included: 77 patients.

**Diagnosis and main criteria for inclusion:**
To be eligible, all subjects were to have chronic non-infectious uveitis disease, and to have completed the study CL3-78989-002 (EYEGUARD™-B), or X052130/CL3-78989-005 (EYEGUARD™-A) or X052131/CL3-78989-006 (EYEGUARD™-C), or were receiving a gevokizumab treatment as compassionate use.

**Test drug:**
Gevokizumab (S 78989) 60 mg subcutaneous (SC) injection, administered every 4 weeks (Q4W) from Week 0 to Week 92 for a total of 24 injections during the study.
Batch No. L0051029, L0054621, L0058198, L0055035.

**Comparator:**
Not applicable.

**Duration of treatment**
Active treatment period: 96 weeks (1 subcutaneous injection every 4 weeks until W92).
Follow-up period: safety follow-up visit at W108.

**Criteria for evaluation:**
***Efficacy measurements:***
Not applicable.

***Safety measurements***
- Adverse events assessment
- Vital signs (peripheral blood pressure, heart rate, body weight, body temperature)
- Standard 12-lead electrocardiogram (ECG)
- Chest X-ray (frontal and lateral)
- Laboratory parameters
- Intraocular pressure
- Other ophthalmologic parameters (including BCVA, vitreous haze, anterior chamber and fundus assessment)

The study was performed in accordance with the ethical principles stated in the Declaration of Helsinki that were consistent with ICH GCP guidance and the applicable regulatory requirement(s). The safety of the drug was assessed by multiple subject assessments of vital signs, physical exams, clinical tests and laboratory evaluations. Concomitant medications and adverse events were monitored and tracked.

**Statistical methods:**
SAFETY ANALYSES
Descriptive statistics in the Safety Set were provided.

**SUMMARY - CONCLUSIONS**

DISPOSITION OF PATIENTS AND ANALYSIS SETS

| | | **Gevokizumab 60 mg (N = 77)** |
|---|---|---|
| **Included** | **Nobs** | **77** |
| In conformity with the protocol | n (%) | 64 (83.1) |
| With protocol deviation(s) before or at inclusion | n (%) | 13 (16.9) |
| **Withdrawn due to** | **N (%)** | **77 (100)** |
| Adverse event | n (%) | 1 (1.3) |
| Withdrawal non-medical reason | n (%) | 5 (6.5) |
| Study discontinuation due to Sponsor decision* | n (%) | 71 (92.2) |

*N : number of patients in the group*
*n : number of patients related to the status*
*% : (n/Nobs)*100 (Nobs: number of included patients)*
**Sponsor decision to discontinue the study was unrelated to safety, but to the fact that primary endpoint was not reached in EYEGUARD B.*

The study was prematurely discontinued following a Sponsor's decision unrelated to safety (primary endpoint not achieved in EYEGUARD B). At that time, 77 patients were included (16 from EYEGUARD B, 28 from EYEGUARD A and 33 from EYEGUARD C) and 71 were on-going at the time of the Sponsor's decision. Of them, 26 patients were on placebo during the previous study, 20 patients were on gevokizumab 30 mg and 31 patients were on gevokizumab 60 mg.

**SUMMARY – CONCLUSIONS (Cont'd)**

DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

A total of 71 patients (92.2%) were withdrawn from the treatment due to Sponsor's decision to prematurely discontinue the study. Before this decision, 6 patients (7.8%) were withdrawn from treatment: 5 patients (6.5%) for non-medical reason and 1 patient (1.3%) for adverse event. None of the included patients completed the study.

BASELINE CHARACTERISTICS

At inclusion (*i.e.* inclusion visit of the previous studies), in the Safety Set (N = 77 patients), the mean ± SD age was 40.7 ± 12.9 years ranging from 18 to 72 years. Around half of the patients (39 patients, 50.7%) were men. Before entering in one of the previous studies, the majority of patients were diagnosed with idiopathic uveitis (35 patients, 45.5%) or Behçet's disease uveitis (30 patients, 39.0%).

EXTENT OF EXPOSURE

In the Safety Set, the treatment duration ranged between 28 and 420 days with a mean (± SD) of 162.4 ± 113.1 days (median of 140.0 days, *i.e.* about 4.6 months).

EFFICACY RESULTS

Not applicable.

SAFETY RESULTS

- **Adverse events**

**Overall summary for adverse events in the Safety Set**

| | | **Gevokizumab 60 mg (N = 77)** |
|---|---|---|
| Patients having reported | | |
| at least one adverse event | n (%) | 42 (54.5) |
| at least one treatment-related adverse event | n (%) | 6 (7.8) |
| Patients having experienced | | |
| at least one serious adverse event | n (%) | 11 (14.3) |
| at least one treatment-related serious AE | n (%) | 1 (1.3) |
| Patients with treatment withdrawal | | |
| due to an adverse event | n (%) | 1 (1.3) |
| due to a serious adverse event | n (%) | - |
| due a treatment-related adverse event | n (%) | 1 (1.3) |
| due a treatment-related serious adverse event | n (%) | - |
| Patients who died | n (%) | - |

During the study, in the Safety Set, 42 patients (54.5%) reported at least one adverse event.

The most frequently affected (≥ 10% of patients) system organ classes (SOC) were eye disorders (21 patients, 27.3%), infections and infestations (14 patients, 18.2%), and investigations (13 patients, 16.9%).

The most frequently reported AEs (> 5% of patients) were uveitis (7 patients, 9.1%), macular oedema (5 patients, 6.5%), Behçet's syndrome*, intraocular pressure increased, Mycobacterium tuberculosis complex test positive and nasopharyngitis (each in 4 patients, 5.2%).
**Note: "Behçet's disease syndrome" referred to worsening of ocular or non-ocular Behçet's disease manifestations and is part of "vascular disorder" according to MedDRA dictionary.*

Regarding adverse events of specific interest (anaphylactic reaction hypersensitivity, malignancies including lymphoma, autoimmune disorders, infections and leukopenia): 17 patients (22.1%) reported 28 AEs related to infections, 8 patients (10.4%) reported 12 events related to autoimmune disorders, 5 patients (6.5%) reported 6 AEs related to allergies and 1 patient (1.3%) reported leukopenia. The most frequently reported AEs (in more than 2 patients) were uveitis (7 patients, 9.1%), nasopharyngitis and mycobacterium tuberculosis complex test positive (each in 4 patients, 5.2%). No emergent active tuberculosis was reported during the study.

**SUMMARY – CONCLUSIONS (Cont'd)**
**SAFETY RESULTS (Cont'd)**

During the study in the Safety Set, adverse events were mainly mild or moderate. Few AEs were reported as severe (12 AEs, 8.2%).

Also few patients reported at least one treatment-related AE according to the investigator (6 patients [7.8%]: blood triglycerides increased, injection site pain, seborrhoeic keratosis, headache, Mycobacterium tuberculosis complex test positive and Tuberculosis [which was in fact gastrointestinal BD worsening, see below] in 1 patient, mouth ulceration and oral pain in 1 patient).

No death was reported during the study.
During the study in the Safety Set, 11 patients (14.3%) experienced at least one serious adverse event, with no specific pattern. Two SAEs in 1 patient were related to the study drug according to the investigator (mycobacterium tuberculosis complex test positive and tuberculosis). However, follow up information indicated that this patient was not diagnosed finally as having tuberculosis but a gastrointestinal BD worsening. None of the serious AEs led to study drug withdrawal.

During the study, one patient had an adverse event (headache) that led to premature treatment discontinuation.

Regarding ophthalmological assessment, no safety issues were observed.

- **Laboratory tests**

As concerns clinical laboratory evaluation, no relevant changes across visits was detected on the mean values of biochemical and haematological parameters. Nevertheless, results should be interpreted with caution as the number of evaluated patients differed from one visit to another.

PCSA biochemical and haematological values were sparse for each parameter.

- **Other safety evaluation**

One clinically significant abnormality (COPD at inclusion) was reported for Chest X-ray.

**CONCLUSION**

**This uncontrolled, open-label, international, extension safety study conducted in patients with chronic non-infectious uveitis disease who completed EYEGUARD™-B, EYEGUARD™-A or EYEGUARD™-C studies, or were receiving a gevokizumab treatment as compassionate use, was prematurely discontinued following a Sponsor's decision unrelated to safety (primary endpoint of EYEGUARD B was not reached). Patients were exposed to gevokizumab 60 mg every 4 weeks for 5 months on average (min 0.9 month ; max 14 months). Seventy seven (N=77) patients were included (16 from EYEGUARD B, 28 from EYEGUARD A and 33 from EYEGUARD C), and 71 patients were on going at the time of the Sponsor's decision to discontinue the study. No safety issue was raised. Gevokizumab was well tolerated. No efficacy conclusion could be drawn since this was not the goal of the study.**

**Date of the report:** 09 June 2016

**Version of the report:** Final version