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| *Document title* | **ABBREVIATED CLINICAL STUDY REPORT SYNOPSIS**<br>**A randomised, double-blind, placebo-controlled proof-of-concept study of the efficacy of gevokizumab 60 mg subcutaneously every 4 weeks over 24 weeks in the treatment of patients with polymyositis, dermatomyositis or necrotizing autoimmune myopathy* disease**<br>***(Necrotizing Autoimmune Myopathy was added by Amendment No. 5)** |
| *Test drug code* | **S78989 (Gevokizumab)** |
| *Indication* | **Polymyositis / Dermatomyositis / Necrotizing Autoimmune Myopathy** |
| *Development phase* | **Phase II** |
| *Protocol code* | **CL2-78989-010** |
| *Study initiation date* | **23 September 2013** |
| *Study completion date* | **25 November 2015** |
| *Main coordinator* | [redacted] |
| *Sponsors* | **Institut de Recherches Internationales Servier (I.R.I.S.)**<br>**50 rue Carnot, 92284 Suresnes Cedex - France**<br>**Laboratorios Servier, S.L.**<br>**Departamento de Investigacion y Desarrollo**<br>**Avenida de los Madronos, 33, 28043 Madrid - Spain**<br>**Servier Laboratories, Ltd, Gallions**<br>**Wexham Springs, Wexham, SL3 6RJ - United Kingdom**<br>**International Centre for Therapeutic Research**<br>**Servier Laboratories (Australia) Pty Ltd**<br>**8 Cato Street, Hawthorn, Victoria 3122 - Australia** |
| *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* | **1 August 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:** Not applicable<br>**Name of Active Ingredient:**<br>Gevokizumab (S 78989) | | |
| **Individual Study Table Referring to Part of the Dossier** | **Volume:** | **Page:** |

**Title of study:** A randomised, double-blind, placebo-controlled proof-of-concept study of the efficacy of gevokizumab 60 mg subcutaneously every 4 weeks over 24 weeks in the treatment of patients with polymyositis, dermatomyositis or necrotizing autoimmune myopathy* disease.
** necrotizing autoimmune myopathy was added by Amendment No. 5*

Protocol No.: CL2-78989-010
EudraCT No.: 2012-005772-34
The description of the study protocol given hereafter includes the modifications of the 5 substantial amendments to the protocol.

**International coordinator**: [redacted]

**Study centres:**
In all, 13 centres located in 7 countries included 27 patients: 1 centre in Belgium (1 patient included), 3 centres in Brazil (7 patients included), 1 centre in Czech republic (6 patients included), 2 centres in Germany (3 patients included), 1 centre in Hungary (1 patient included), 3 centres in Italy (6 patients included), 2 centres in Spain (3 patients included).

**Publication (reference):** Not applicable.

| **Studied period:** | **Phase of development of the study:** |
|---|---|
| Initiation date: 23 September 2013 (date of first visit first patient)<br>Completion date: 25 November 2015 (date of the last visit of the last patient**)** | phase II |

**Objectives:**

The objective of this study was to evaluate the efficacy and safety of gevokizumab in adult patients with polymyositis (PM), dermatomyositis (DM), or necrotizing autoimmune myopathy* (NAM*) intolerant or resistant or dependent to systemic oral corticosteroids.
** NAM disease was added by Amendment No. 5*

In order to increase knowledge on gevokizumab in the PM/DM/NAM patients, concentration of gevokizumab (*i.e.* free S78989) in serum was to be measured in all patients for further population pharmacokinetic (PK) analysis.

Antidrug Antibodies (ADA) (if any) were also to be assessed in all patients.

Furthermore, other assessments including cytokine assays, pharmacogenomics (PGx), and other omics (*i.e.* protenomics and metabonomics) were to be performed. As well, retrospective analysis on co-medication, other biomarkers and/or biological parameters of interest that may have been identified later could have been performed if necessary.

**Methodology:**
This was a phase II proof-of-concept, international, multi-centre, randomised, double-blind, placebo-controlled study over 24 weeks, followed by an open-label period over 24 weeks as added by Amendment No. 2 (except for France, as added by Amendment No. 3), designed to evaluate the efficacy and safety of gevokizumab in patients (male or female aged ≥ 18 years) with PM, DM or NAM, intolerant or resistant or dependent to systemic oral corticosteroids (CS).

The treatment randomisation and allocation were centralised using an Interactive Web Response System (IWRS) procedure. The treatment (gevokizumab or placebo) was assigned at inclusion visit by a balanced, non-adaptive randomisation with stratification on the disease (PM, DM or NAM).

**Methodology (Cont'd):**
According to investigator's judgment, the double-blind period was to be followed by an open-label 24-week period (except for France, as added by Amendment No. 3) with gevokizumab 60 mg administered subcutaneously (SC) every 4 weeks (Q4W).

*Following an in-house Sponsor's decision (general strategic and business reasons unrelated to safety), the study was discontinued prior to all patients having completed the double-blind period. In this specific context, an abbreviated clinical study report was written.*

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

**Number of patients:**
Planned: approximately 40 patients to be included (20 receiving gevokizumab, 20 placebo).
Included: 27 patients (14 in the gevokizumab 60 mg group and 13 in the placebo group).

*Due to difficulties in recruitment of such rare diseases and the exploratory nature of the study, the Sponsor decided to end the recruitment in July 2015 with 27 patients included/randomised into the stud (less than the targeted 40 patients).*

**Diagnosis and main criteria for selection/inclusion:**
Patients were to be male or female, aged ≥ 18 years (or legal age of majority in the country) with probable or PM, DM, or NAM diagnosed according to 119th European NeuroMuscular Centre (ENMC) classification, intolerant or resistant or dependent to systemic oral corticosteroids (CS), with a disease diagnosis duration ≤ 6 years (the duration of 6 years was changed to 10 years by Amendment No. 3, and then the entire criterion was deleted by Amendment No. 5), active disease (worsening or progressive muscle weakness) with an Manual Muscle Testing (MMT-8) score on proximal muscles and neck flexors no greater than 85/110 at selection and inclusion visits.

**Test drug:**
S78989 (gevokizumab) 60 mg: one subcutaneous (SC) injection every 4 weeks (Q4W) during 24 weeks (double-blind period), and, as added by Amendment No. 2 during 24 additional weeks until W48 (second period: open-label period). Batch No.: L0045751, L0051029.

**Comparator (Reference product and/or placebo):**
Matching placebo: one subcutaneous injection every 4 weeks during 24 weeks (double-blind period).

**Rescue therapy for worsening:**
In case of worsening, the investigator had to stop the study drug and the patient had to be prescribed the most appropriate therapy according to the best accepted customary practices.
In addition, the investigator could have decided to stop the study drug for any other reason, according to his judgment. In both cases, the patient could nevertheless continue to be followed until the end of the study without study drug. A complete withdrawal visit had to be performed when patients stopped the study drug.

**Duration of treatment:**
**Run-in period:** 2 weeks (that could be extended) from ASSE to W0,
**Active treatment period:**

- First period: 24 weeks (double-blind period, one SC injection Q4W from W0 to W20).
- Second period (added by Amendment No. 2): 24 weeks (follow-up open-label period, one SC injection Q4W from W24 to W44).
  France did not participate in the open-label period of the study.

**Criteria for evaluation:**
All the measurements (efficacy, safety, etc.) to be performed after the W24 visit (*i.e.* between W28 and W44) were added following the introduction by Amendment No. 2 of an open-label period of 24 weeks after the end of the planned double-blind 24-week period.

***Efficacy measurements:***
Primary efficacy endpoint
The primary efficacy endpoint was the clinical improvement according to Manual Muscle Testing (MMT-8) on the proximal muscles and neck flexors score, defined as an increase of 15% or more in the score.
MMT-8 score was evaluated at ASSE, W0, W4, W8, W12 W16, W20, W24, W32, W40, W48 visits (and withdrawal visit).
Patients who worsened during the study were considered as with no clinical improvement.

**Criteria for evaluation (Cont'd):**

***Safety measurements:***

- Adverse events (AEs), assessed at each visit,
- Laboratory parameters (haematology panel, biochemistry panel) assessed by a central laboratory and urinalysis, at each visit,
- Clinical examination and vital signs including blood pressure (BP) (systolic/ diastolic), pulse rate, weight and body temperature, assessed at each visit (height was measured at ASSE visit only).
- Standard 12-lead electrocardiogram (ECG), performed at ASSE, W24 and W48 visits (and withdrawal visit).
- Chest X-ray performed at ASSE (only for patients who had not had a chest X-ray within the previous 12 weeks), W24 (only for patients who had not had a chest X-ray within the previous 4 weeks as added by Amendment No. 2 and except for United Kingdom patients who had performed the open-label period as added by Amendment No. 3) and W48 visits (and withdrawal visit).

***Other measurements not specifically related to efficacy or safety:***

Due to the Sponsor's decision to discontinue the study (general strategic and business reasons unrelated to safety), the PK, ADA, cytokines blood samples, PGx, other omics assessments and retrospectives analyses initially planned were not performed (samples were destroyed).

**Statistical methods:**

***Analysis Set:***
All statistical analyses planned were performed only on the Safety Set (*i.e.* all patients having taken at least one dose of IMP during the double-blind treatment period (between W0 and W20 included), as there was no difference between the Included Set (IS), the Randomised Set (RS) and the Safety Set (SS).

***Efficacy analysis:***
*Primary endpoint:*
For the primary efficacy endpoint, the number and percentage of patients with clinical improvement according to MMT-8 at W24 (or last observation carried forward [LOCF] during the double-blind treatment period were provided by treatment group and by class of disease (PM, DM and NAM), in the SS.

Due to the context of the study other efficacy endpoints were not analysed (biomarkers such as creatine phosphokinase (CPK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were described in the safety analysis).

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

***Pharmacokinetic analysis***: Due to the context of the study, no planned PK analyses were performed (samples destroyed).

**SUMMARY - CONCLUSIONS**

DISPOSITION OF PATIENTS AND ANALYSIS SETS

| | Gevokizumab 60 mg | Placebo | All |
|---|---|---|---|
| | **n** | **n** | **n** |
| **Included** | **14** | **13** | **27** |
| DM | 8 | 9 | 17 |
| NAM | 3 | 2 | 5 |
| PM | 3 | 2 | 5 |
| **Withdrawn due to** | **7** | **3** | **10** |
| adverse event** | 1 | - | 1 |
| non-medical reason | 6 | 3 | 9 |
| *Lost to follow-up* | - | - | - |
| **Completed the double-blind period** | **7** | **10** | **17** |
| **On-going in the open-label period*** | 15 | NA | 15 |
| **Withdrawn due to** | **9** | **NA** | **9** |
| non-medical reason | 9 | NA | |
| *Lost to follow-up* | - | NA | |
| **Completed the open-label period** | 6 | NA | 6 |
| | | | |
| **Randomised Set (RS)** | **14** | **13** | **27** |
| **Safety set (SS)** | **14** | **13** | **27** |
| **Open Label Safety Set (OLSS)** | **15** | **NA** | **15** |

** During the open-label period, all patients (whatever their treatment group during the double-blind period) were under gevokizumab 60 mg. Two patients did not enter the open-label period as they had stopped the IMP before W24 and continued in the study without treatment until W24.*

*n: Number of patient*

***It should be noted that 3 patients had an adverse event that led to premature IMP discontinuation. For 2 of them, the adverse event did not lead to study withdrawal (these patients continued in the study without treatment), the third one was withdrawn from the study due to the adverse event.*

*DM: Dermatomyositis; NAM: Necrotizing Autoimmune Myopathy; PM: Polymyositis*

Overall, 4/27 patients (14.8%) reported a total of 6 protocol deviations *before or at inclusion* (one patient in the gevokizumab 60 mg group *versus* 3 patients in the placebo group). These deviations concerned ECG not carried-out, biological samples not taken and unauthorised treatment. *After inclusion*, 18/27 patients (66.7%) reported a total of 45 protocol deviations **during the double-blind period** (10/14 patients *versus* 8/13 patients, respectively in the gevokizumab 60 mg and placebo groups). The most frequent deviation concerned study treatment (12 deviations in 11 patients overall *i.e.* 40.7%). No relevant difference between groups was observed. *After W24*, 7/15 patients (46.7%) reported a total of 12 protocol deviations after inclusion **during the open-label period** in the gevokizumab 60 mg group. Protocol deviations were mainly related to questionnaires not reported or not completed, ECG not carried out and "study treatment duration between 2 visits > x days" (3 patients each).

BASELINE CHARACTERISTICS

*It should be noted that all results presented in this abbreviated report should be interpreted with caution due to the low number of patients in each group of the Safety Set (N = 14 or 13 patients).*

At selection, age of patients ranged from 27 to 60 years, with a mean age of 46.2 ± 10.4 years (median = 46 years). Most of the patients were female (70.4%) in accordance with the sex-ratio observed in PM and DM diseases, and were Caucasian (85.2%). No relevant difference between the 2 groups was observed.

Regarding the studied diseases, DM reached approximately 2/3 of the patients (63.0%), and PM and NAM were diagnosed each in 18.5% of patients, without relevant difference between groups. The duration of the disease since diagnosis was longer in the gevokizumab 60 mg group (median = 5.0 years) than in the placebo group (median = 2.0 years). As regards response to oral corticosteroid administration at baseline, 18/27 patients were corticodependent and 6/27 were intolerant, without relevant difference between groups. The remaining patients (3/27; all in the gevokizumab 60 mg group) were resistant to oral corticosteroids.

**SUMMARY – CONCLUSIONS (Cont'd)**

BASELINE CHARACTERISTICS (Cont'd)

At **inclusion**, all the patients of the Safety Set received at least one concomitant treatment. Patients received mostly corticosteroids for systemic use (24/27 patients, 88.9%), mostly prednisone (17/27 patients, 63.0%), vitamins (20/27 patients, 74.1%), mostly cholecalciferol (16/27 patients, 59.3%) and immunosuppressants (19/27 patients, 70.4%), mostly methotrexate (11/27 patients, 40.7%). The main concomitant treatments received by patients during the **double-blind treatment period** were similar to those received at inclusion.
During the **open label treatment period**, all patients received at least one concomitant treatment. They were mainly corticosteroids for systemic use (all patients) mostly prednisone (10/15 patients, 66.7%) and vitamins (11/15 patients, 73.3%).

EXTENT OF EXPOSURE

In the Safety Set, during the **double-blind period**, treatment duration ranged between 54 and 173 days with a median duration of 167.0 days. The treatment duration was shorter in the gevokizumab 60 mg group (median = 126.5 days) than in the placebo group (median = 168.0 days).
In the OLSS, during the **open-label period**, treatment duration under gevokizumab 60 mg ranged between 28 and 168 days with a median duration of 118.0 days.

FOLLOW-UP

Over the whole study, 6/27 patients had at least one worsening of their disease (according to the protocol definition) since the previous visit: 4/14 patients in the gevokizumab 60 mg group and 2/13 patients in the placebo group.

EFFICACY RESULTS

In the specific context of the study (study discontinuation), only descriptive statistics for the primary efficacy endpoint (clinical improvement according to MMT-8) were provided for the Safety Set.

**Primary assessment endpoint: Clinical improvement**

In the Safety Set, 5/14 patients (35.7%) in the gevokizumab 60 mg group *versus* 7/13 patients (53.9%) in the placebo group showed a clinical improvement* during the double-blind treatment period (see the table below for more details for DM, NAM and PM diseases).

**defined as patients with an increase of global score for MMT (Manual Muscle Test) ≥ 15% relative to baseline, and no clinical worsening during the double-blind treatment period.*

**Number and percentage of patients with clinical improvement during the double-blind treatment period - Safety Set**

| Clinical improvement | | | Gevokizumab 60 mg (N = 14) | Placebo (N = 13) |
|---|---|---|---|---|
| No | | n (%) | 9 (64.3) | 6 (46.2) |
| **Yes** | | **n (%)** | **5 (35.7)** | **7 (53.9)** |
| All | | n (%) | 14 (100) | 13 (100) |
| Dermatomyositis | No | n (%) | 5 (62.5) | 5 (55.6) |
| | **Yes** | **n (%)** | **3 (37.5)** | **4 (44.4)** |
| | All | n (%) | 8 (100) | 9 (100) |
| Necrotizing Autoimmune Myopathy | No | n (%) | 2 (66.7) | 1 (50.0) |
| | **Yes** | **n (%)** | **1 (33.3)** | **1 (50.0)** |
| | All | n (%) | 3 (100) | 2 (100) |
| Polymyositis | No | n (%) | 2 (66.7) | - |
| | **Yes** | **n (%)** | **1 (33.3)** | **2 (100)** |
| | All | n (%) | 3 (100) | 2 (100) |

*N: Number of patients by group.*
*n: Number of patients.*
*%: (n/N) x 100.*

SAFETY RESULTS

- **During the double-blind treatment period**

***Emergent adverse events***

**Overall summary for adverse events over the double-blind period (W0-W24) in the Safety Set (N = 27)**

| | | Gevokizumab 60 mg (N = 14) | Placebo(N = 13) |
|---|---|---|---|
| Patients having reported | | | |
| at least one emergent adverse event | n (%) | 12 (85.7) | 10 (76.9) |
| at least one treatment-related emergent adverse event | n (%) | 5 (35.7) | 2 (15.4) |
| Patients having experienced | | | |
| at least one serious adverse event (including death) | n (%) | 3 (21.4) | 1 (7.7) |
| at least one serious emergent adverse event (including death) | n (%) | 3 (21.4) | 1 (7.7) |
| at least one treatment-related emergent serious adverse event | n (%) | - | - |
| Patients with treatment withdrawal | | | |
| due to an emergent adverse event | n (%) | 3 (21.4) | - |
| due to an emergent serious adverse event | n (%) | 1 (7.1) | - |
| due a treatment-related emergent adverse event | n (%) | - | - |
| Patients who died | n (%) | - | - |

*N: Number of patients in each treatment group, n: Number of patients, %: (n/N)x100*

Due to the low number of patients in the gevokizumab 60 mg and placebo groups results should be interpreted with caution.

During the **double-blind treatment period** (W0-W24) in the Safety Set, the number of patients who reported at least one **emergent adverse event** (EAE) showed no relevant difference between gevokizumab 60 mg group (12/14 patients, 85.7%) and placebo group (10/13 patients, 76.9%).

The most frequently affected (in at least 5 patients) system organ classes (SOCs) in the gevokizumab 60 mg group were musculoskeletal and connective tissue disorders (6/14 patients, 42.9%) and infections and infestations (5/14 patients, 35.7%). These SOCs were also the most frequently reported in the placebo group (4/13 patients, 30.8% and 5/13 patients, 38.5% respectively), and showed no relevant difference between groups.
The frequency of other system organ classes tended to be affected at a similar frequency in both groups, except gastrointestinal disorders which appeared to be slightly more frequent in the gevokizumab 60 mg group (4/14 patients, 28.6%) than in the placebo group (1/13 patients, 7.7%). As previously mentioned, the results should be interpreted with caution because of the small number of patients in each group.

In the gevokizumab 60 mg group, EAEs were each reported by one patient, except arthralgia, nasopharyngitis, muscular weakness and nausea, each reported by 2 patients. In the placebo group, each EAE was reported once.

No **severe** EAE was reported during the double-blind period.

A total of 5/14 patients in the gevokizumab 60 mg group reported 7 EAEs **considered to be related to the study drug** according to investigator's opinion (pneumonia, tonsillitis, migraine and 2 events of nausea and nasopharyngitis) *versus* 2/13 patients in the placebo group who reported 4 EAEs considered to be related to the study drug (herpes virus infection, fatigue and 2 headaches). None of these events were judged as serious. All patients recovered.

During the double-blind treatment period, 3 patients (all in the gevokizumab 60 mg group) experienced a total of 3 EAEs leading to **treatment withdrawal**: 2 patients had muscular weakness (non-serious) and one patient had a worsening of polymyositis (serious). These 3 events were considered as not related to study drug and the patients recovered or were recovering.

The proportion of **unresolved** events was low in both groups (14.6% of EAEs [*i.e.,* 6/41 EAEs] *versus* 14.7% [*i.e.* 5/24 EAEs], respectively). Of them, one was judged serious, (upgraded by the sponsor: diabetes mellitus) and all were considered as not related to study drug/protocol.

SAFETY RESULTS (Cont'd)

In all, a total of 23 EAEs of **specific interest** (12 in the gevokizumab 60 mg group and 11 in the placebo group) were reported during the double-blind treatment period: 4 events (3 events reported by 2 patients in the gevokizumab 60 mg group *versus* one event reported by one patient in the placebo group) related to *anaphylactic reaction/hypersensitivity*, 17 events (8 events reported by 5 patients *versus* 9 events reported by 5 patients, respectively) related to *infection* and 2 events (one in each group) related to *autoimmune disorders*. All resolved or were resolving. In the gevokizumab 60 mg group, 4 specific events related to *infection* (in 3/14 patients) were considered as related to the study drug according to the investigator (tonsillitis, pneumonia and 2 events of nasopharyngitis) and one EAE related to *autoimmune disorders* was judged as serious (worsening of polymyositis). In the placebo group, one specific event related to *infection* was considered as related to the study drug (herpes virus infection) and none was judged serious.

During the double-blind period, 4/27 patients reported a least one **serious** EAE (SEAE): 3/14 patients in the gevokizumab 60 mg group reported 3 serious EAEs (worsening of polymyositis, diabetes mellitus [seriousness upgraded by the Sponsor], ovarian adenoma) and one patient in the placebo group reported spinal pain and vertebrobasilar insufficiency. All these serious events were considered as not related to the study drug, and all resolved/resolving except diabetes mellitus.

No **death** occurred during the double-blind period.

***Laboratory tests***
Biochemical and haematological emergent **PCSA values** under treatment during the double-blind treatment period were sparse in all treatment groups except for low lymphocytes in the gevokizumab 60 mg group (5/14 patients, 35.7% in the gevokizumab 60 mg group *versus* 1/13 patients, 7.7%, in the placebo group).
*(No PCSA limits were defined for CPK and MCV).*

***Other safety evaluation***
During the double-blind treatment period, neither relevant change nor difference between groups was observed regarding **vital signs** and **clinical examination**, and no emergent abnormality according to the investigator was reported for **ECG** and **chest X-ray**.

- **During the open-label period in the Open-Label Safety Set**

***Adverse events***

**Overall summary for adverse events over the open-label period (after W24 visit included) in the Open-Label Safety Set (N = 15)**

| | | Gevokizumab 60 mg (N = 15) |
|---|---|---|
| Patients having reported | | |
| at least one adverse event | n (%) | 7 (46.7) |
| at least one treatment-related adverse event | n (%) | 2 (13.3) |
| Patients having experienced | | |
| at least one serious event (including death) | n (%) | 1 (6.7) |
| at least one treatment-related serious adverse event | n (%) | - |
| Patients with treatment withdrawal | | |
| due to an adverse event | n (%) | - |
| Patients who died | n (%) | - |

*N: Number of patients the treatment group, n: Number of patients, %: (n/N)x100*

During the **open-label period** (after W24 included) all the patients (15) were to receive gevokizumab 60 mg. Among them, 7 patients (46.7%) reported at least one adverse event in the Open-Label Safety Set.
The most frequently affected system organ class (SOC) reported was infections and infestations (5 AEs in 3 patients, 20.0%). All AEs experienced during the open-label period were reported once except lymphopenia reported twice (in one patient).
Overall, 3 severe adverse events were reported in one patient (pharyngeal abscess complicated with sepsis and lymphopenia). All these events were judged serious by the investigator, and were considered as not related to the study drug/protocol. The patient recovered.

During the open-label period, 2/15 patients reported each one adverse event considered to be **related to the treatment**: one sinusitis bacterial and one neutropenia. None of these events was judged serious or severe by the investigator. The patient with neutropenia did not recover according to the last information available. No adverse event **led to treatment withdrawal.**

SAFETY RESULTS (Cont'd)

Most of the AEs resolved/were resolving (22/26 AEs *i.e.* 84.6% of the AEs) while 4 AEs (headache, fatigue, vomiting, neutropenia) did not resolve. These 4 **unresolved** AEs were non-serious and all except one (neutropenia) were considered as not related to the study drug by the investigator.
In all, a total of 13 AEs of **specific interest** were reported during the open-label period: 3 events in one patient related to *anaphylactic reaction/hypersensitivity*, 5 events in 3 patients related to *infection*, 3 events in 2 patients related to *leukopenia* and 2 events in 2 patients related to *malignancies including lymphoma*). Among these AEs, 2 related to *infections* and one related to *leukopenia* (*i.e.*, pharyngeal abscess complicated with sepsis and lymphopenia) in the same patient were judged serious. In addition, 2 AEs of specific interest were considered as related to the study drug according to the investigator: one in the class of *infection* (sinusitis bacterial) and one in the class of *leukopenia* (neutropenia). All events resolved except one neutropenia according to last information available.

One patient experienced a total of 5 **serious** AEs (SAEs) (haematuria and pharyngeal abscess complicated with sepsis, lymphopenia and coagulopathy), considered as not related to the study drug according to the investigator, and which resolved.

No **death** occurred during the open-label period.

***Laboratory tests***
During the open-label period on gevokizumab 60 mg, the most frequent biochemical PCSA values were low HDL cholesterol and high ALT (high ALT values from 3.2 ULN to 5.3 ULN) both reported by 3 patients (20.0%); other PCSA biochemistry values were sparse. Regarding PCSA haematological values it should be noted that 4/15 patients (26.7%) had low PCSA values of lymphocytes.
*(No PCSA limits were defined for CPK and MCV).*

***Other safety evaluation***
Due to the decreasing number of patients over time during the open-label period, results should be interpreted with caution: no relevant change from W24 to the end of the 2nd part of the study (W48 visit) was observed regarding **clinical examination** and **vital signs**.
No **ECG** abnormality was reported according to the investigator. With regards to **chest X-rays**, one patient had an abnormality at W24 visit (blurred right basal - probably dystelechtasiac, not present at baseline) considered as not clinically significant by the investigator.

**CONCLUSION**
**This international, multicentre, randomised, phase II proof-of-concept, double-blind, placebo-controlled study was planned over 24 weeks (followed by an open-label period over 24 weeks) to evaluate the efficacy and safety of gevokizumab 60 mg SC every 4 weeks in 40 adult patients with polymyositis, dermatomyositis, or necrotizing autoimmune myopathy intolerant or resistant or dependent to systemic oral corticosteroids. Due to difficulties in recruitment for such rare diseases and the exploratory nature of the study, the Sponsor decided to end the recruitment with 27 patients included, less than the 40 initially foreseen. Following the Sponsor's decision to discontinue the study for general strategic and business reasons (unrelated to safety), the double-blind period was not fully completed (around 2/3 of the patients completed the double-bind period).**
**Due to the low number of included patients, results should be interpreted with caution. However, there was no clear indication of clinical improvement according to MMT-8 that could be attributable to gevokizumab treatment.**
**No relevant difference between gevokizumab and placebo groups was observed during the double-blind period regarding the number of emergent adverse events, including adverse events of specific interest; 3 patients in the gevokizumab (none in the placebo group) reported an adverse event leading to treatment withdrawal. All adverse events of specific interest reported during the open-label period resolved except one neutropenia. Five patients in the gevokizumab 60 mg group and one in the placebo group during the double-blind period and a quarter of patients during the open-label period had potentially clinically significant low abnormal values of lymphocytes. Overall, no safety concern was raised over the study.**

**Date of the report:** 1ST August 2016

**Version of the report:** Final version