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:** S78989 (Gevokizumab)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: An exploratory, open-label, single centre, phase II, proof of concept study of gevokizumab treatment in patients with Schnitzler syndrome. Protocol No.: CL2-78989-018 EudraCT No.: 2013-002562-39 The description of the study protocol given hereafter includes the modifications of the two substantial amendments to the protocol.		
Investigator: [redacted]		
Study centre: [redacted]		
Publication (reference): Not applicable		
Studied period: Initiation date: 05 December 2013 (first visit first patient) Completion date: 04 January 2016 (last visit last patient)	**Phase of development of the study:** Phase II	
Objective: The objective of the study was to explore the efficacy and safety of gevokizumab in patients with Schnitzler syndrome. In order to increase knowledge of gevokizumab in Schnitzler syndrome patients, serum concentrations of gevokizumab were measured in all patients for further population pharmacokinetic (PK) analyses and investigation of any PK/PD relationship. Anti-Drug Antibodies (ADA; if any) were also assessed in all patients. Furthermore, other assessments including biological markers, bone markers, cytokines and inflammatory protein assays were performed.		
Methodology: This study was an exploratory, single-centre, open-label, phase II, proof of concept study. This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.		
Number of patients: Planned: up to 5 patients Included: 3 patients		
Inclusion criteria Males or females aged ≥ 18 years (weight between 45 and 125 kg) with diagnosis of definite or probable Schnitzler syndrome using the Strasbourg criteria (Simon *et al.*, 2013) at least one year prior, and with active Schnitzler syndrome disease as defined by the composite score of the presence of at least 2 of 3 clinical criteria (from rash, fever (defined as ≥ 38°C) and bone or arthritis pain) and elevated CRP levels ≥ 30 mg/L, and without clinical signs and symptoms of pulmonary and extra-pulmonary tuberculosis disease (X-ray performed within 12 weeks prior to selection).		

Test drug:
Gevokizumab: subcutaneous (SC) administration. (at a concentration of 60 mg/mL for each vial).
Each 60 mg single dose was to be administered as one SC injection of 1 mL, and up to 3 vials containing 60 mg/mL were to be used for each administration (depending on the dose administered to each patient).

Administration schedule was as follows (including Amendment No 1):
A loading dose of 180 mg SC (x3 injections of 60 mg spaced closely apart) given at D0, followed by four administrations of 60 to 180 mg every 4 weeks (Q4W) or earlier if deemed necessary by the investigator upon disease symptoms (with an interval of at least 14 days (2 weeks) between each gevokizumab administration and a maximum-authorised dose of 180 mg per 2-week period), then upon the rhythm of gevokizumab administration established during the initial administration phase (*i.e*. during the first 4 administrations). Lower doses of gevokizumab (minimum of 60 mg) could be administered from the 5th injection in the case of an adequate response according to the investigator's judgment or re-increased thereafter depending on clinical evaluation of the response.
Of note: the 3 patients included in the study were recruited prior to the changes related to the Amendment No 1. Consequently, none of included patients started at loading dose of 180 mg; they all started at an initial treatment dose of 60 mg as stated in the initial study protocol.

Batch No: L0045751, L0054620, L0054621, L0051029

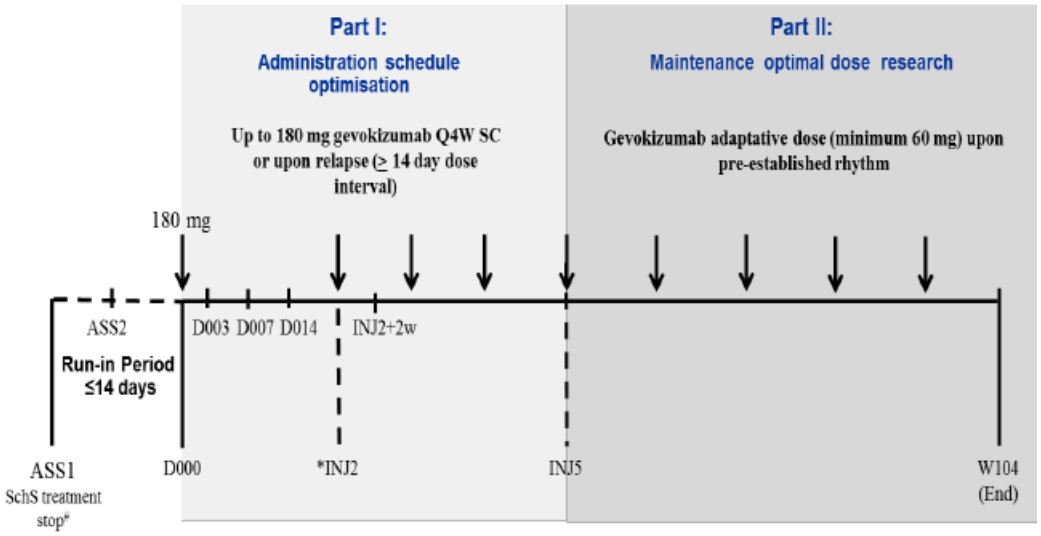
Comparator (Reference product and/or placebo):
Not applicable

Duration of treatment:
Run-in period: up to 14 days, no active treatment.
From pre-selection visit ASS1 to inclusion visit D0, a run-in period was dedicated to the confirmation of patient eligibility. Previous treatment for Schnitzler syndrome had to be discontinued on or after the pre-selection (ASS1) visit depending on biological results. Patients experiencing relapse of disease symptoms attended then the selection visit (ASS2) where the inclusion/non-inclusion criteria were verified, notably clinical signs and symptoms related to Schnitzler syndrome and CRP levels. Patients fulfilling the inclusion criteria then attended the D0 inclusion visit (which could be performed on the same day as the ASS2 visit if all inclusion criteria were satisfied).

Active treatment period: the duration of the open-label gevokizumab SC treatment was extended from 1 to 2 years (W104) by Amendment No 2 (October 2014) with a total maximum-authorised monthly dose of 360 mg during the part I *(i.e.* until the 4th injection inclusive), followed during the part II by the possibility of a lower dose (minimum 60 mg) thereafter according to clinical evaluation of the response, administered monthly or upon the rhythm of the first administration phase if shorter. From the 8th injection onwards in patients whose response was stable, the subsequent gevokizumab administrations might have occurred in accordance with a delay considered as suitable according to the investigator judgment.

Duration of treatment: (Cont'd)

Study plan (including Amendments No 1 and No 2)



#*Previous treatment for Schnitzler syndrome could be ceased at ASS1 or later if patient was pre-selected.*
**For patients experiencing disease symptoms, INJ2 could occur at D014 or between D014 and a maximum of 28 days following the initial gevokizumab injection.*
Note: Injection schedule (arrows) in Part II not represented to scale.

Criteria for evaluation:
Efficacy measurements:

- Clinical symptoms related to Schnitzler syndrome (SchS)

Skin rash, fever and [bone or arthritis pain] were scored as follows: 0 = none, 1 = minimal, 2 = some and 3 = considerable.

- Assessment of response to gevokizumab treatment: the patient's composite clinical and biological response was assessed according to the investigator as 'complete', 'partial' or 'no response'. A complete response was defined by the absence of clinical symptoms related to SchS or minimal disease activity, and a decrease in CRP levels (≥ 50% from baseline or ≤ 10 mg/L).
- Patient and physician global assessment (PGA):
  - Physician Global Assessment (PhGA): in relation to question "According to your clinical evaluation, how do you find your patient today in comparison to before starting treatment " the investigator assessed the patient's overall status by selecting the most appropriate reply from either "markedly improved", "moderately improved", "slightly improved", "no change", "slightly worsened", "moderately worsened" or "markedly worsened".
  - Patient Global Assessment (PaGA): the patient was asked to answer a question on his/her own in relation to his/her overall assessment in order to compare his/her condition to baseline, and to select a reply from the following: "markedly improved", "moderately improved", "slightly improved", "no change", "slightly worsened", "moderately worsened" or "markedly worsened".
- Quality of Life assessment: SF-36 patient-reported outcome questionnaire was administered and completed by the patient on his/her own.
- Assessment of biological markers and cytokines:
  - CRP (C-Reactive Protein).
  - Paraprotein: monoclonal immunoglobulin IgG or IgM.
  - Inflammatory proteins: calprotectin and serum amyloid A (SAA).
  - Cytokines: IL-1α, IL-1β, IL-6, IL-1Ra, IFN-γ, IL-17, IL-18, TNFα.
  - Markers of bone remodelling: osteoprotogerin (OPG), receptor activator of nuclear factor kappa-β ligand (RANKL), bone-specific–alkaline phosphatase (bALP), C-terminal telopeptide-1 (CTX-1) and pro-collagen type 1 amino-terminal pro-peptide (P1NP) as well as vascular endothelial growth factor (VEGF).

Criteria for evaluation: (Cont'd)

Pharmacokinetic (PK) and ADA measurements

As only 3 patients were included, only individual serum concentrations were provided. Impact of immune response to gevokizumab (*i.e.* production of ADA, if any) on the PK was explored.

Safety measurements (at each visit):

- Occurrence of emergent adverse events (EAE) including EAE of special interest.
- Haematology and biochemistry blood parameters, urinalysis.
- Vital signs including temperature, weight, systolic and diastolic blood pressure.
- 12-lead ECG parameters and chest X-ray (at pre-selection and final visits).

Statistical methods:

Analysis Set:

Both efficacy and safety analysis were performed in the Safety Set which was defined as all patients having taken at least one dose of Investigational Medicinal product (IMP).

Efficacy analysis:

Level of hs-CRP was drawn at baseline and each post-baseline visit on the D000-W104 period and by patient.
Values of other efficacy endpoints, such as complete and partial response, clinical symptoms relative to Schnitzler syndrome (skin rash, fever, bone or arthritis pain), Physician Global Assessment and Patient Global Assessment were presented at each visit in individual listings.

Safety analysis:

Descriptive statistics were provided for emergent adverse events and blood laboratory parameters. Vital signs, clinical examination, ECG and Chest X-ray were described by individual data listings.

Pharmacokinetic analysis:

Gevokizumab PK parameters were not calculated. Only individual serum concentrations were finally provided.

SUMMARY - CONCLUSIONS

A total of 3 patients, a [redacted] male and two females, [redacted], were included and received at least one injection of gevokizumab. All completed the 2-year study follow-up. No protocol deviation was detected before or at inclusion, while 2 patients reported 8 protocol deviations during the study. Schnitzler syndrome was diagnosed since a mean of 64.0 months (range of 18.0 to 135 months).

Before study entry, all patients were receiving an interleukin-1 inhibitor *i.e.* anakinra. At inclusion, paracetamol and antihistamines for systemic use (cetirizine or levocetirizine) were on-going in 2 patients.

Treatment duration was around 2 years with a mean of 23.7 months and ranged between 23.2 and 24.1 months. All included patients received a starting dose of 60 mg. The highest maintenance dose was 180 mg per 2-week period in two patients and 60 mg per 2-week period in one patient.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS

For all patients, **response to treatment** (composite of clinical and biological response) was assessed as either partial or complete at each visit over the 2-year treatment period:

- Partial response: 12/40 visits for patient No. 1, 22/36 visits for patient No. 2, 18/33 visits for patient No. 3.
- Complete response: 28/40 visits for patient No. 1, 14/36 visits for patient No. 2, 15/33 visits for patient No. 3.

The **physician global assessment** showed improvement from 3 days after the first injection with fluctuating magnitude of improvement over the 2-years but was mainly reported as either moderately or markedly improved.

- Slightly improved: 2/40 visits for patient No.1, 8/36 visits for patient No.2, 2/33 visits for patient No. 3.
- Moderately improved: 13/40 visits for patient No. 1, 20/36 visits for patient No. 2, 11/33 visits for patient No.3.
- Markedly improved: 25/40 visits for patient No. 1, 8/36 visits for patient No. 2, 20/33 visits for patient No. 3.

The **patient global assessment** showed improvement at most visits from 3 days (2 patients) to 7 days (1 patient) after the first injection.

One week after the first injection, a decrease in **hs-CRP** levels was observed for all patients and, from 2 weeks after the first injection these **hs-CRP** levels were lower than 50% of baseline values. Over the 2-years of treatment, hs-CRP values were either maintained at low levels (with normalised values for one patient) or fluctuated with peak values.

SAFETY RESULTS

All patients experienced at least one EAE with a total of 52 reported EAEs over the 2-year treatment period. Diarrhoea, viral upper respiratory tract infection and gastrointestinal viral infection affected 2 patients, and the other preferred terms affected 1 patient. No specific preferred term was affected. 3 EAEs (in 2 patients) were considered as related to the IMP among diarrhoea, upper respiratory tract infection and bacterial respiratory tract infection. Regarding EAE of specific interest for safety evaluation listed in the protocol, 17 non-serious infections in 3 patients were reported. No signs of allergies or anaphylaxis were reported.
All EAEs were non-serious, except one EAE upgraded as serious by the Sponsor (cervical dysplasia).

Blood laboratory tests showed one emergent Potentially Clinically Significant Abnormal value (PCSA) value in 2 patients: low albumin and high platelet count. The high platelet count observed was probably in correlation with variable inflammation levels (measured with CRP).

CONCLUSION

This was an exploratory open-label, single centre, phase II study to explore the efficacy and safety of gevokizumab in patients with Schnitzler syndrome diagnosed at least one year previously.
Gevokizumab was administered to 3 patients with starting dose of 60 mg, and were to receive maximum dose of 180 mg per 2-week period. Patients were closely followed during 2 years.

For all patients, response to treatment (composite of clinical and biological parameters) was assessed as either partial or complete at each visit over the 2-year treatment period. The physician global assessment showed improvement from 3 days after the first injection with fluctuating magnitude of improvement over the 2 years, but was mainly reported as moderately or markedly improved. The patient global assessment showed improvement from 3 to 7 days after the first injection and for almost all visits over 2 years.

One week after the first injection, a decrease in hs-CRP levels was observed for all patients and, from two weeks after the first injection, these levels were lower than 50% of baseline values. Over the 2-years of treatment, hs-CRP values were either maintained at low levels or fluctuated with peak values.
There was no serious EAE except one EAE upgraded as serious by the Sponsor (cervical dysplasia). Regarding adverse events of specific interest for safety evaluation as listed in the protocol, 17 non-serious infections were reported in 3 patients. No signs of allergies or anaphylaxis were reported. There was no safety concern.

Date of the report: 20 July 2016

Version of the report: Final version