Document title	**ABBREVIATED CLINICAL STUDY REPORT SYNOPSIS**
Study title	**A randomisEd, double-masked, placebo-controlled studY of the Efficacy of GevokizUmAb in the tReatment of patients with Behçet's Disease Uveitis** **The EYEGUARD™-B study**
Test drug code	**S 78989 (Gevokizumab)**
Indication	**Uveitis associated with Behçet's Disease**
Development phase	**Phase III**
Protocol code	**CL3-78989-002**
Study initiation date	**14 November 2012**
Study completion date	**29 September 2015**
Main coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France** **Les Laboratoires Servier - Representative Office** **Paveletskaya Square 2, building 3** **Moscow 115 054 – Russia**
Responsible medical officers	[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	**20 April 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:** **Name of Active Ingredient:** Gevokizumab S 78989		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: A randomisEd, double-masked, placebo-controlled studY of the Efficacy of GevokizUmAb in the tReatment of patients with Behçet's Disease Uveitis
The EYEGUARD™-B study.

Protocol No.: CL3-78989-002
EudraCT No.: 2012-001125-27
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 13 countries included 84 patients: Armenia (1 centre, 6 patients), Brazil (1 centre, 2 patients), Germany (4 centres, 6 patients), Greece (1 centre, 7 patients), Hong-Kong (1 centre, 1 patient), Israel (2 centres, 3 patients), Italy (3 centres, 7 patients), Portugal (1 centre, 2 patients), Russia (1 centre, 2 patients), South Korea (6 centres, 21 patients), Tunisia (1 centre, 1 patient), Turkey (5 centres, 24 patients), United-Kingdom (2 centres, 2 patients).

Publication (reference): Not Applicable

Studied period:	**Phase of development of the study:**
Initiation date: 14 November 2012 Completion date: 29 September 2015 – Study discontinuation (Sponsor's decision)	Phase III

Objectives:
The primary objective of this study was to demonstrate the superiority of gevokizumab as compared to placebo on top of current standard of care in reducing the risk of Behçet's disease uveitis exacerbations.

The secondary objectives were to assess the effect of gevokizumab on the other efficacy endpoints and to evaluate its safety.
In addition, the pharmacokinetic of gevokizumab and the formation of Anti-Drug Antibodies (ADA), if any, were assessed.

Methodology:
This was a prospective, international, multicentre, randomised, double-masked, placebo-controlled, parallel group, event-driven trial (Core study-Part 1), followed by a one year extension (double masked extension – Part 1), continued by an open long-term (8-month period) safety follow-up (Part 2). This study was conducted in patients having an history of Behçet's disease uveitis with ocular involvement of the posterior segment, who had experienced at least 2 ocular exacerbations within the 18 months prior to selection, with the most recent having occurred within the last 4 months and having been treated successfully with high dose corticosteroids (CS).

This was a non-adaptive, centralised, balanced block randomisation with stratification on the number of previous exacerbations within 18 months (= 2 or > 2) and gender.

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

At the end of the Core study period, the study discontinuation was decided owing to Sponsor's decision, (primary endpoint not achieved). Consequently the Part 1-double masked extension period had been prematurely stopped and the open long-term safety follow-up period (Part 2) was not carried on.

Number of patients (Core study was event-driven):
Planned: Approximately 60 patients (modified by Amendment No. 2), 30 in each arm (number of patients depended on first ocular exacerbation incidence).
Included in the Randomised Set of the Core study (*i.e.* when the 29 first ocular exacerbations had occurred): 83 patients (40 patients in the gevokizumab group and 43 patients in the placebo group). One additional patient was randomised after the end of the Core study period in the gevokizumab group.

Diagnosis and main criteria for inclusion:
To be eligible, all subjects were to have a history of Behçet's disease with ocular involvement of the posterior segment, and to have experienced at least 2 ocular exacerbations within the 18 months prior to selection, with the most recent having occurred within the last 4 months and having been treated successfully with high dose CS. At study entry, patients had to be receiving immunosuppressive therapy (azathioprine [AZA] ≤ 2.5 mg/kg/day, mycophenolate mofetil [MMF] ≤ 3 g/day / mycophenolate sodium [MPS] ≤ 2.16 g/day, cyclosporine-A [CSA] and/or methotrexate [MTX] ≤ the highest tolerable dose, alone or in any combination) stable for at least 6 weeks prior to randomisation, and oral dose of corticosteroids (20 mg/day equivalent oral prednisone), stable for at least 1 week prior to randomisation.

Test drug:
Gevokizumab (S 78989) 60 mg subcutaneous (SC) injection, administered every 4 weeks (Q4W) on top of background treatments.
Batch No. L0045751, L0054621, L0051029.

Comparator:
Matching placebo subcutaneous (SC) injection, administered every 4 weeks (Q4W) on top of background treatments.

Duration of treatment (as planned)

Run-in period: 10 days between selection and inclusion during which no study treatment was dispensed.

Treatment periods:

- Part 1 – double masked period, which consisted in:
  - *The Core study*: this part of the study was event-driven, based on the time to first acute ocular exacerbation (primary endpoint). The Core study ended when the target number of exacerbations had occurred. The maximum follow-up duration of the Core study could be extended up to 3 years.
  - *A double-masked extension period* at the end of the Core study (*i.e.* when the target number of ocular exacerbations had occurred):
    - For patients who did not exacerbate during the Core study and tolerated the study drug well, treatment was still administered in double-mask for an additional year.
    - For patients who exacerbated during the Core study but tolerated the study drug well, a rescue therapy was proposed and:
      - Either the patients still received double-masked treatment for the whole duration of Part 1 while adjusting background therapy (dose and/or drug, as appropriate) within the predefined group of drugs described at inclusion or,
      - Depending on the investigator's opinion, stopped the double-masked study treatment and received the most appropriate background therapy according to best usual practices. These patients were to be followed until the end of Part 1 (this part of the study was prematurely stopped).
- Part 2 – open long-term safety follow-up period (separate report): at the end of the double-masked extension period, all patients who tolerated well the study drug continued to receive gevokizumab in open-label condition for a further 8-month period (this part of the study was not carried on).

Criteria for evaluation:
Efficacy measurements:
Primary endpoint
Time to first acute ocular exacerbation, defined as the number of days from randomisation to the first acute ocular exacerbation, over the Core study period (main analysis).

Definition of acute ocular exacerbation for purposes of assessing the risk reduction of exacerbations:
Any of the following compared to baseline in either eye:
- Worsening in vitreous haze (VH), with or without anterior chamber cell involvement, by a 2-unit change on a scale of 0 to 4+ (SUN) (*patients with a VH score of 3+ who worsened to 4+ were considered to have exacerbated).*
- ≥ 15-letter ETDRS decrease in BCVA not explained by a cause other than ocular inflammation secondary to Behçet's disease.
- Emergence of retinal infiltrates or acute retinal vasculitis.

Ocular observations at defined visit and ocular exacerbations if any were to be documented by Fundal photographs.

Main secondary endpoints
- Ocular exacerbations.
- Visual Acuity.
- Vitreous haze.
- Retinal infiltrates or acute retinal vasculitis.

Safety measurements
- Adverse clinical events.
- Laboratory parameters including hs-CRP.
- Non-ocular manifestations of Behçet's disease.
- Intra-ocular pressure.
- Vital signs (sitting blood pressure and heart rate, temperature, body weight).
- Chest-X-ray, ECG.

Statistical methods:
EFFICACY ANALYSES
- **Primary endpoint: acute ocular exacerbation**
  In the FAS (based on Intention To Treat principle)
  - *Main analysis*
    Time to first acute ocular exacerbation, defined as the number of days from randomisation to the first acute ocular exacerbation before any rescue therapy. For patients withdrawn from the study drug, only exacerbations occurring until 28 days (+ 5 day window) after the last study drug injection and before any rescue therapy were included in the main analysis: a Cox's proportional hazard model adjusted for the number of previous exacerbations within 18 months and gender, was used to compare the time to first exacerbation between groups. The hazard ratio estimate as well as its 95% CI and the associated p-value were provided.
    Censoring rules:
    - According to the protocol, no patient was expected to be rescued before the first exacerbation. Any subject rescued prior to his first exacerbation was censored for the main analysis at the time of the rescue therapy.
    - Patients who were definitively withdrawn from the study drug and without occurrence of exacerbation until 28 days (+5 day window) after the last study drug injection were censored at this date.
    - Patients lost to follow-up were censored at their last assessment date.
    - Patients with no ocular exacerbation at the end of the Core study were censored at the date of the occurrence of the twenty-nine exacerbation for the Core study analysis.

Statistical methods:
EFFICACY ANALYSES (Cont'd)

- **Primary endpoint: acute ocular exacerbation (Cont'd)**
  - *Sensitivity analyses*: the same model as the main analysis was performed taking into account the following censoring rules:
    - Sensitivity to rescue therapy: rescued patients prior to any exacerbation were considered as having an exacerbation at the time of rescue therapy.
    - Sensitivity to study drug withdrawal: patients definitively withdrawn from the study drug due to an adverse event and without occurrence of exacerbation were considered as having an exacerbation at the date of withdrawal.
    - Sensitivity analysis to compliance with the protocol: the main analysis was also performed in the Per Protocol Set (PPS).

- **Secondary endpoints**
  - The number of ocular exacerbations per patient over the Core study period was compared between treatment groups using a Poisson regression model adjusted for stratification factors as covariates and taking into account the length of follow-up. The frequency of recurrence was expressed for the two treatment groups in terms of recurrences per 100 patient*years.
  - The Best Corrected Visual Acuity (BCVA): gevokizumab was compared to placebo on the change from baseline to D168 (or LOCF if D168 was missing), using a general linear model with baseline, number of previous exacerbations within 18 months and gender as covariates. The estimate of between treatment group difference with its standard error, its 95% confidence interval and the associated p-value were provided.
  - Vitreous haze score (VH): the same analysis as for BCVA was performed.
  - For other parameters, descriptive statistics were provided by treatment group.

SAFETY ANALYSES
Descriptive statistics in the Safety Set were provided by treatment group.

SUMMARY - CONCLUSIONS
DISPOSITION OF PATIENTS AND ANALYSIS SETS

Status		Gevokizumab	Placebo	All
Included (randomised)				
Core study	**n**	**40**	**43**	**83**
In compliance with the protocol	n (%)	23 (57.5)	31 (72.1)	54 (65.1)
With a protocol deviation before or at inclusion	n (%)	17 (42.5)	12 (27.9)	29 (34.9)
Part 1	**n**	**41**	**43**	**84***
In compliance with the protocol	n (%)	24 (58.5)	31 (72.1)	55 (65.5)
With a protocol deviation before or at inclusion	n (%)	17 (41.5)	12 (27.9)	29 (34.5)
Withdrawn from treatment due to				
Core study	**n (%)**	**9 (22.5)**	**10 (23.3)**	**19 (22.9)**
Adverse event	n (%)	5 (12.5)	4 (9.3)	9 (10.8)
Protocol violation	n (%)	-	2 (4.7)	2 (2.4)
Lack of efficacy	n (%)	-	2 (4.7)	2 (2.4)
Withdrawal non-medical reason	n (%)	4 (10.0)	2 (4.7)	6 (7.2)
Part 1	**n (%)**	**41 (100)**	**42 (100)**	**83** ** **(100.00)**
Study discontinuation	n (%)	32 (78.1)	20 (47.6)	52 (62.7)
Adverse event	n (%)	5 (12.2)	8 (19.1)	13 (15.7)
Protocol violation	n (%)	-	2 (4.8)	2 (2.4)
Lack of efficacy	n (%)	-	3 (7.1)	3 (3.6)
Withdrawal non-medical reason	n (%)	4 (9.8)	9 (21.4)	13 (15.7)
Withdrawn from study due to				
Core study	**n (%)**	**7 (17.5)**	**5 (11.6)**	**12 (14.5)**
Adverse event	n (%)	1 (2.5)	1 (2.3)	2 (2.4)
Protocol violation	n (%)	-	1 (2.3)	1 (1.2)
Withdrawal non-medical reason	n (%)	6 (15.0)	3 (7.0)	9 (10.8)
Part 1	**n (%)**	**41 (100)**	**43 (100)**	**84 (100)**
Study discontinuation	n (%)	34 (82.9)	34 (79.1)	68 (81.0)
Adverse event	n (%)	1 (2.4)	3 (7.0)	4 (4.8)
Protocol violation	n (%)	-	2 (4.7)	2 (2.4)
Withdrawal non-medical reason	n (%)	6 (14.6)	4 (9.3)	10 (11.9)
Analysis Sets during the Core study period				
Randomised Set		**40**	**43**	**83**
Full Analysis Set (FAS)		**40**	**43**	**83**
Per Protocol Set (PPS)		**31**	**35**	**66**
Analysis Sets during the Part 1				
Randomised Set		**41**	**43**	**84***
Safety Set		**41**	**43**	**84**

%: Expressed as percentage of the randomised patients
**One patient was included and randomised in the gevokizumab group after the end of the Core study period*
***for one patient (No. 002 792 3405 00048), the investigator did not tick the box « status stopped », in fact 84 patients were withdrawn from treatment.*

At the end of the Core study period (*i.e.* when the 29 first ocular exacerbations had occurred, N = 83), the study discontinuation was decided due to sponsor's decision, based on unachievement of the primary endpoint. Consequently the Part 1-double masked extension period was prematurely stopped and the open long-term safety follow-up period (Part 2) was not carried on as planned initially.

A total of 83 patients were included and randomly assigned in the Core study to one of the 2 groups: 40 patients in the gevokizumab group and 43 patients in the placebo group. Two countries were major contributors: Turkey with 24 randomised patients and South Korea with 21 randomised patients.
One additional patient was included and randomised in the gevokizumab group after the 29 first ocular exacerbations; *i.e.* after the end of the Core study period.
All randomised patients (*i.e.* 84 patients) received at least one dose of study drug during the study.

SUMMARY – CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

During the Core study, a total of 19 patients (22.9%) were withdrawn from treatment with a similar proportion in the two groups: 9 patients [22.5%] in the gevokizumab group and 10 patients [23.3%] in the placebo group. Reasons for withdrawal were also similar in both groups: mainly for adverse event (5 patients [12.5%] and 4 patients [9.3%] respectively) and non-medical reason (4 patients [10.0%] and 2 patients [4.7%] respectively).

The patient included and randomised in the gevokizumab group after the end of the Core study period was taken into account in the Part I analyses but not in the Core study. The present report focuses on results of the Core study for study outcome and efficacy analyses and on results of the Part 1 for safety analyses.

BASELINE CHARACTERISTICS

At selection, in the Randomised Set of the Core study (N = 83), the mean ± SD age was 34.7 ± 9.5 years, ranging from 18 to 67 years. Patients were mostly men (72.3%). Overall, 69.9% of patients were White and 26.5% were Asian. Overall no relevant difference between groups was observed.

Concerning the characteristics of Behçet's disease, the mean duration from the diagnosis of Behçet's disease was longer in the gevokizumab group (mean: 52.6 ± 55.8; median: 40.5 months) than in the placebo group (mean: 43.1 ± 56.4, median: 26.0 months). As required by the study protocol, all but one patient included in the study fulfilled the IUSG classification criteria for Behçet's disease at selection (one patient had only 2 out of the 3 criteria required). Regarding Behçet's disease non-ocular symptoms, all patients reported recurrent oral ulcers since diagnosis, 77.1% reported skin lesions and 61.5% reported arthritis findings. Other symptoms were less common.

As regards uveitis associated with Behçet's disease, all randomised patients had either panuveitis (60.0% in the gevokizumab group and 65.1% in the placebo group) or posterior uveitis (40.0% and 34.9%, respectively) at selection as required by the protocol, with a mean duration of uveitis longer in the gevokizumab group (mean: 54.5 ± 54.3 months, median: 41.5 months) than in the placebo group (mean: 40.0 ± 52.3 months, median: 21.0 months) and a mean time from last exacerbation of 2.3 months ± 1.0 month (median: 2.0 months) in both groups. The mean number of ocular exacerbations having occurred within 18 months before randomisation was similar in both groups (2.6 ± 0.8 and 2.9 ± 1.2, respectively).

At inclusion and during the treatment period, all patients received systemic corticosteroids and all but one (in the placebo group) received in addition an immunosuppressive therapy (mainly azathioprine and cyclosporine A).

As concerns the main ophthalmological parameters at baseline, in the index eye (eye having experienced the last exacerbation before randomisation), almost all patients, whatever the group, presented with a quiescent ocular inflammatory status: the BCVA score by ETDRS was quite good with approximately 70 letters in both groups. A slightly greater mean score in the gevokizumab group than in the placebo group (73.1 ± 14.7 letters *versus* 69.3 ± 15.4 letters, respectively) was observed.

Overall, the majority of patients (78.3%) had a vitreous haze SUN score of 0 or 0.5+.
Very few retinal infiltrates (RI) and retinal vasculitis (RV) were present at baseline: each in 1 patient in the gevokizumab group. Most patients had no sign of inflammation in the anterior chamber: anterior chamber cells SUN score of 0 (75.9%) or 0.5+ (20.5%).

Similarly, ophthalmological findings observed in the contralateral eye showed a quiescent inflammatory status for almost all patients, with no relevant differences between groups.

EXTENT OF EXPOSURE

The treatment duration over the Part 1, assessed in the Safety Set (N = 84), was longer in the gevokizumab group (median: 473.0 days, *i.e.* 15.5 months) than in the placebo group (median: 369.0 days, *i.e.* 12.1 months). The compliance was satisfactory, with an overall mean compliance of 107.1 ± 5.6% (monthly SC injection done at the investigator's site).
Of note, the mean duration of treatment over the Core study (*i.e.* when the 29th ocular exacerbation had occurred) was 400.8 ± 267.4 days (median: 369 days, *i.e.* 12.1 months: 391.0 days in the gevokizumab group and 337.0 days in the placebo group).

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

- **Primary assessment criterion**

Time to first acute ocular exacerbation over the Core study period
Between-group comparison in the FAS (N = 83)

		Gevokizumab (N = 40)	Placebo (N = 43)
	Total number of patients at risk (N)	40	43
	n (%)*	14 (35.0)	15 (34.9)
	NPY (n)	24.47	20.81
	PY (%)	57.2	72.1
	Mean time to 1st exacerbation** (days)	119.1	95.3
Main analysis			
Multiple Cox model	E (SE) [1]	0.85 (0.32)	
	95% CI [2]	[0.41 ; 1.77]	
	p-value [3]	0.661	
Sensitivity analyses			
Sensitivity to rescue therapy			
Multiple Cox model	E (SE) [1]	0.79 (0.24)	
	95% CI [2]	[0.44 ; 1.42]	
	p-value [3]	0.435	
Sensitivity to withdrawal			
Multiple Cox model	E (SE) [1]	0.78 (0.29)	
	95% CI [2]	[0.38 ; 1.61]	
	p-value [3]	0.494	
Sensitivity to compliance (PPS)			
Multiple Cox model	E (SE) [1]	0.91 (0.38)	
	95% CI [2]	[0.41 ; 2.05]	
	p-value [3]	0.826	

**: Total number of patients having a first ocular exacerbation during the Core study period*
NPY: Total number of patients-year at risk
PY: Events/NPY x 100 annual incidence rate, number of patients having an acute ocular exacerbation for 100 patients-year at risk
***: In patients having an acute ocular exacerbation*
1: Estimate (Standard Error) of the adjusted Hazard Ratio of the first exacerbation between treatment groups: gevokizumab versus placebo
2: 95% Confidence Interval of the estimate
3: p-value (multiple Cox regression model with the number of previous exacerbations within 18 months and gender as covariates)
Sensitivity to rescue therapy: rescued patients prior to any exacerbations were considered as having an exacerbation at the time of rescue therapy.
Sensitivity to withdrawal: patients definitively withdrawn from the study drug due to adverse event and without occurrence of exacerbation were considered as having an exacerbation at the date of withdrawal.

Gevokizumab did not significantly affect the exacerbations: the estimated hazard ratio was 0.85 (0.32) (95% CI = [0.41 ; 1.77], p= 0.661).
The number of patients with a first ocular exacerbation during the Core study period in the FAS was similar in the 2 groups: 14 patients in the gevokizumab group (35.0%) and 15 patients in the placebo group (34.9%). Four ocular exacerbations were bilateral in the placebo group *versus* none in gevokizumab group. However, the annual incidence rate of the first ocular exacerbation was lower in the gevokizumab group than in the placebo group (57.2% *versus* 72.1%, for 24 and 21 patient-years at risk, respectively). The presence of emergent retinal infiltrates and/or acute retinal vasculitis alone was the most frequent component of these first ocular exacerbations, as it concerned 50% and 47.4% of patients, respectively in the gevokizumab group and the placebo group. The association of several components was less frequent in the gevokizumab group (2 out of 14 patients in the FAS) than in the placebo group (7 out of 15 patients in the FAS). Sixty five percent (54/83) of patients were free of exacerbation, with a similar proportion in both groups.
Similar results were observed in the PPS.

SUMMARY - CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

- **Secondary assessment criteria**

As regards the secondary criteria, the total number of acute ocular exacerbations having occurred during the Core study period in the FAS was 33 *versus* 39 exacerbations, respectively in the gevokizumab group *versus* placebo group corresponding to a mean number of 0.8 ± 1.1 *versus* 1.0 ± 1.3 exacerbations, respectively, with no statistically significant difference between groups. However, the annual incidence rate was slightly lower in the gevokizumab group than in the placebo group (70.0% *versus* 81.5%, for 47 and 48 patient-years at risk, respectively). As for the 29 first exacerbations described above, the most common component of ocular exacerbations was, in both groups, the emergence of retinal infiltrates/vasculitis (51.4% in the gevokizumab group and 54.2% in the placebo group). The association of several components was less frequent in the gevokizumab group (12.5%) than in the placebo group (32.6%). Bilateral exacerbations were less frequent in the gevokizumab group compared to placebo: 6.1% (2 exacerbations) *versus* 23.1% (9 exacerbations), respectively.
Overall, more than 50% of patients were free of ocular exacerbation (53.9% [21 patients] in gevokizumab group and 53.7% [22 patients] in placebo group.)

In the index eye, visual acuity (assessed by BCVA) over the baseline-D168 treatment period remained stable in the gevokizumab group while it tended to deteriorate in the placebo group: the mean change in BCVA score from baseline to D168 was -0.1 ± 12.2 letters in the gevokizumab group *versus* -3.6 ± 13.8 letters in the placebo group, with a statistically significant between-groups difference estimated at 2.86 letters (1.33) (95% CI = [0.21 ; 5.51], p = 0.035). Consistently, the rate of patients with BCVA worsening (≥ 10 letters) was statistically significantly lower in the gevokizumab group as compared to the placebo group (10.3% [4 patients] *versus* 26.8% % [11 patients]) (OR = 0.29, 95% CI = [0.07 ; 0.99], p = 0.048). Similar trends without statistical significance were observed in favor of gevokizumab for the rate of patients with a BCVA improvement ≥ 10 letters and the rate of patients with a BCVA improvement ≥ 15 letters.

As regards the VH SUN score in the index eye, no relevant changes in the mean score were observed between baseline and D168 in both treatment groups (0.15 ± 0.67 in the gevokizumab group and 0.15 ± 0.77 in the placebo group), as well as no relevant between-group differences (E(SE) = -0.02(0.16)).

Emergent RI and RV in the index eye were less frequent in the gevokizumab group than in the placebo group (21.1% *versus* 29.3%, respectively for RI and 10.3% *versus* 26.8%, respectively for RV).

Regarding OCT parameters in the index eye, the incidence of emergent macular oedema (local reading) in the index eye over the Core study was twice lower in the gevokizumab group than in the placebo group (4 patients [10.3%] *versus* 7 patients [18.0%], respectively).

No relevant changes in the mean Fundus Fluorescein Angiography (FFA central reading) total score and the mean cell and flare scores from baseline to each post baseline assessment were observed, in both treatment arms.

Concerning the other emergent ophthalmological parameters (hypopyon, papillitis, neovascularization of disk and neovascularization elsewhere) during the Core study, hypopyon and neovascularization were slightly less frequent in gevokizumab group (1/39 patients [2.6%] in the gevokizumab group *versus* 4/41 [9.8%] in the placebo group, for both parameters) in the index eye.

Regarding rescue therapy, 21 patients (52.5%) in the gevokizumab group and 25 patients (58.1%) in the placebo group received at least one rescue therapy over the Core study period in the FAS. The total number of rescue therapies prescribed during the Core study was approximately twice lower in the gevokizumab group (52 rescue therapies) *versus* placebo group (90 rescue therapies). Reasons for rescue were mainly for per protocol exacerbation in both groups (55.8% in the gevokizumab group and 55.6% in the placebo group). Patients in gevokizumab group were less likely (approximately 2 times) to be rescued for macular oedema (13.5%) than in the placebo group (27.8%), while ocular and non-ocular Behçet's disease were more frequently a reason in the gevokizumab group (9.6% and 15.4%, respectively) than in the placebo group (2.2% and 1.1%, respectively).

Slightly more patients in the gevokizumab group (19 patients [47.5%]) than in the placebo group (16 patients [37.2%]) reached and maintained the 5 mg daily dose of corticosteroids for 3 months before any rescue therapy.
Similar trends were observed in the contralateral eye.
Results observed in the PPS showed similar trends as those observed in the FAS.
During the Part 1 of the study in the FAS, results were also similar as those observed over the Core study period.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

- **Emergent adverse events**

Overall summary for adverse events in the Safety Set (Part 1 – N = 84)

		Gevokizumab (N = 41)	Placebo (N = 43)
Patients having reported at least one:			
Emergent adverse event	n (%)	38 (92.7)	40 (93.0)
Treatment-related emergent adverse event	n (%)	7 (17.1)	8 (18.6)
Patients having experienced at least one:			
Serious adverse event	n (%)	14 (34.1)	15 (34.9)
Emergent serious adverse event	n (%)	13 (31.7)	14 (32.6)
Treatment-related serious EAE	n (%)	1 (2.4)	-
Patients with treatment withdrawal due to:			
Emergent adverse event	n (%)	2 (4.9)	7 (16.3)
Emergent serious adverse event	n (%)	1 (2.4)	4 (9.3)
Treatment-related emergent adverse event	n (%)	-	-
Treatment-related emergent serious adverse event	n (%)	-	-
Patients who died	n (%)	-	-

In the Safety Set of Part 1 study (N = 84), the incidence of patients presenting with at least one EAE was similar in the gevokizumab group (92.7%) and in the placebo group (93.0%).

The most frequently affected (≥ 15 patients) system organ classes (SOC) in both groups were vascular disorders (including "Behçet's syndrome" according to coding medDRA dictionary), infections and infestations, eye disorders and investigations. Vascular disorders were similarly reported in the gevokizumab group and in the placebo group (26 patients [63.4%] and 28 patients [65.1%], respectively), and corresponded mainly to "Behçet's syndrome"; as well as Infections and infestations (21 patients [51.2%] and 20 patients [46.5%], respectively) and Investigations (15 patients [36.6%] and 16 patients [37.2%], respectively). Eye disorders (mainly macular oedema and cataract) were reported less frequently in the gevokizumab group (15 patients [36.6%]) than in the placebo group (30 patients [69.8%]). In addition, gastrointestinal disorders (mainly diarrhoea and nausea) were reported in 16 patients (39.0%) in the gevokizumab group *versus* 13 patients (30.2%) in the placebo group.

The most frequently reported EAEs (≥ 5 patients) in both groups were, with a similar incidence in the 2 groups: "Behçet's syndrome"* (26 patients [63.4%] in the gevokizumab group and 25 patients [58.1%] in the placebo group), headache (8 patients [19.5%] and 6 patients [14.0%]) and nasopharyngitis (6 patients [14.6%] and 6 patients [14.0%]). Diarrhoea, increased intraocular pressure, arthralgia and cataract were also among the most commonly reported events, similarly reported in both groups, (5 patients [12.2%] *versus* 4 patients, [9.3%], respectively for diarrhoea and increased intraocular pressure, 5 patients [12.2%] *versus* 2 patients [4.7%] for arthralgia and 3 patients [7.3%] *versus* 6 patients [14.0%] for cataract). Vision blurred was more frequently reported in the gevokizumab group (5 patients [12.2%]) than in the placebo group (none), and macular oedema was less frequently reported in gevokizumab group (4 patients [9.8%]) than in the placebo group (15 patients [34.9%]).

**Of note*, "Behçet's syndrome" referred to worsening or emergent ocular or non-ocular Behçet's disease manifestations and is part of "Vascular disorders" according to coding medDRA dictionary.

In the Safety Set, the incidence of ophthalmological EAEs (using pre-defined lists) was lower in the gevokizumab group (24 patients [58.5%] with 98 EAEs) than in the placebo group (35 patients [81.4%] with 152 EAEs), mainly explained by a lower rate of macular oedema (4 patients [9.8%] *versus* 15 patients [34.9%], respectively).

No relevant change in mean intraocular pressure between baseline and the last post-baseline measurement over the Part 1 was observed in both groups.

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

- **Emergent adverse events (Cont'd)**

No difference between groups was observed regarding events of specific interest (Malignancies including lymphoma, Autoimmune disorders, Infections, Neutropenia, and Anaphylactic reaction Hypersensitivity), predefined according to known risks of immunosuppressive drugs and monoclonal antibodies: 24 patients (58.5%) in the gevokizumab group and 24 patients (55.8%) in the placebo group reported at least one event. The most frequently reported EAE was nasopharyngitis in 6 patients in each group (14.6% in the gevokizumab *versus* 14.0% in the placebo group).

Emergent adverse events were mainly mild or moderate in the gevokizumab group as well as in the placebo group. The incidence of severe EAEs was slightly lower in the gevokizumab group (16 EAEs, 5.1%) than in the placebo group (30 EAEs, 8.4%).

The incidence of treatment-related EAEs was similar in the gevokizumab group (7 patients, 17.1%) and in the placebo group (8 patients, 18.6%).

No death was reported during the study.

During the Part 1, 13 patients in the gevokizumab group (31.7%) and 14 patients in the placebo group (32.6%) reported serious emergent adverse events. The incidence of SEAEs leading to treatment withdrawal (all were "Behçet's syndrome") was lower in the gevokizumab group than in the placebo group (1 patient [2.4%] and 4 patients [9.3%], respectively). Only one SEAE was related to the study drug (pneumonia in the gevokizumab group, not diagnosed as tuberculosis).

The incidence of emergent (serious and non-serious) adverse events leading to premature treatment withdrawal was lower in the gevokizumab group (2 patients [4.9%]) than in the placebo group (7 patients [16.3%]).

As regards to the non-ocular manifestations of Behçet's disease, no relevant change between baseline and the last post-baseline value on treatment was observed for disease activity assessed by BCDAF questionnaire (mean change = -0.3 ± 2.9 *versus* -0.9 ± 3.3, respectively in the gevokizumab *versus* placebo groups, both median = 0), as well as for patients' perception of their disease, assessed by VAS score (6.0 ± 27.1 mm; median = 1.5 mm *versus* -6.1 ± 22.5 mm; median = -1.0 mm, respectively).

Emergent non-ocular symptoms related to Behçet's disease were reported in 17 patients (41.5%) in the gevokizumab group and 15 patients (34.9%) in the placebo group. They were mainly arthralgia (8 patients [19.5%] and 5 patients [11.6%], respectively) and fatigue (7 patients [17.1%] and 5 patients [11.6%], respectively).

- **Laboratory tests**

As concerns clinical laboratory evaluation during the Part 1, no relevant difference between groups was detected on the mean evolution over time of biochemical and haematological parameters, except for hs-CRP (-2.6 ± 12.2 mg/L in the gevokizumab group *versus* 3.4 ± 6.6 mg/L in the placebo group), GGT (5.9 ± 33.3 IU/L *versus* -6.8 ± 37.5 IU/L, respectively), WBC (-1.9 ± 3.0 G/L *versus* -0.8 ± 3.0 G/L, respectively) and neutrophils (-1.6 ± 2.6 G/L *versus* -0.3 ± 2.5 G/L, respectively).

Emergent PCSA biochemical values were sparse in both groups and for each parameter, without relevant between-group difference.

Emergent PCSA haematological values were sparse in both groups and for each parameter, except for low haematocrit reported in 4 patients (11.1%) in the gevokizumab group (*versus* 1 patient [2.6%] in the placebo group).

- **Other safety evaluation**

Clinical examination (weight, BMI, temperature, sitting HR and sitting blood pressure) did not show any clinically relevant changes over time nor difference between groups.

No emergent clinically significant abnormality was reported for ECG and Chest X-ray.

CONCLUSION

This international Phase III study, conducted in patients with a history of Behçet's disease uveitis with ocular involvement of the posterior segment, aimed to demonstrate the superiority of gevokizumab (60 mg monthly SC injection) as compared to placebo, on top of current standard of care in reducing the risk of Behçet's disease uveitis exacerbations.

Gevokizumab did not significantly affect the exacerbations: the estimated hazard ratio was 0.85 (0.32) (95% CI = [0.41 ; 1.77], p = 0.661). However, data suggested that gevokizumab could preserve visual acuity, reduce the uveitis severity, decrease the emergence of macular oedema, and could have a corticosteroid sparing effect.

Over the whole study period, no safety concern was raised. The safety profile of gevokizumab was similar to the placebo profile.

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