Sponsor Novartis
Generic Drug Name AEB071 (Sotrastaurin)
Therapeutic Area of Trial Uveitis
Approved Indication Investigational
Study Number AEB071A2211
Title A multicenter, single sequence, open-label study to assess the tolerability, safety and efficacy of 2 weeks oral AEB071 300 mg twice daily , followed by 6 weeks AEB071 200 mg twice daily in the treatment of patients with macular edema associated with non-infectious intermediate uveitis, posterior uveitis, or panuveitis
Phase of Development Phase II
Study Start/End Dates 15 July 2008 to 23 Oct 2009
Study Design/Methodology The current study employed an open-label and single treatment sequence design with recruitment of non-infectious uveitis patients in a multi-center setting. All patients received active AEB071.
Centres The current study was conducted in 13 centers located in the United States.
Publication None.

Objectives

Primary objective(s)

To assess the safety and tolerability of AEB071 in the treatment of uveitis

Secondary objective(s)

To investigate how many uveitis patients will have a reduction in uveitis in response to AEB071

Test Product (s), Dose(s), and Mode(s) of Administration

Three AEB071 100 mg capsules (300 mg) orally twice daily for the first two weeks, followed by two AEB071 100 mg capsules (200 mg) orally twice daily for another six weeks.

Reference Product(s), Dose(s), and Mode(s) of Administration

Not applicable.

Criteria for Evaluation

Primary variables

The primary objective of the study was to assess the safety and tolerability of AEB071 from baseline to week 8, in patients with macular edema associated with non-infectious intermediate uveitis, posterior uveitis, or panuveitis.

Secondary variables

The key secondary efficacy variable will be the proportion of responders at week 8.

All efficacy analyses for the key secondary efficacy objective will be performed using the Per Protocol Analysis Set.

Statistical Methods

Primary safety endpoint

Descriptive statistics (n, mean, standard deviation, median and ranges for continuous variables, frequencies and percentages for categorical variables) will be provided where applicable by eye (study and fellow) for all safety and tolerability data. All data will be listed by patient, and where applicable, by eye (study and fellow).

Key secondary efficacy endpoint

Whether the proportion of responders in the AEB071 group from baseline to the end of Week 8 is similar to the proportion of responders in the infliximab historical treatment group; the alternative hypothesis being that the proportion of responders in the infliximab historical treatment group is higher than the proportion of responders in the AEB071 group.

The key secondary efficacy analysis will be performed after Week 8. A 2-group Fisher's exact test will be performed to assess whether the proportion of responders in the AEB071 group is lower than in the infliximab historical group at the 1-sided significance level of 0.05.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key inclusion criteria

- Male and female patients with non-infectious intermediate or posterior uveitis or panuveitis in at least one eye, age 18 to 70 years of age inclusive, who are otherwise in good health
- Macular edema with average central retinal thickness ≥ 250 µm
- A vitreous haze score ≥ 1, but ≤ 3 (based on the National Eye Institute grading system)
- Best Corrected Visual Acuity no worse than 20/400 and no better than 20/40
- Daily prednisone dose ≤ 1 mg/kg

Key exclusion criteria

- Patients with choroidal neovascularization.
- Patients with the following forms of uveitis:
  - Serpiginous choroidopathy
  - Acute multifocal placoid pigment epitheliopathy
  - White dot retino-choroidopathies (e.g., multiple evanescent white dot syndrome (MEWDS) or multifocal choroiditis)
- Macular edema associated with other ocular disease (e.g., diabetic retinopathy)
- Patients who had a prior vitrectomy
- Any eye condition that may affect the evaluation of visual acuity and retinal thickness
- Concurrent use of certain immunosuppressive agents (specific washout periods for different agents are defined in the protocol)
- Use of systemic medications known to be toxic to the lens, retina, or optic nerve (e.g. deferoxamine, chloroquine, and ethambutol) currently or in the past 6 months

Number of Subjects

	AEB071 Treated Subjects
Planned n	15
Treated n	13
Intent-to-treat population (ITT) n (%)	13 (100%)
Completed n (%)	12 (92.3%)
Withdrawn n (%)	1 (7.7%)
Withdrawn due to adverse events n (%)	1 (7.7%)

Demographic and Background Characteristics

	AEB071 Treated Subjects
N (ITT)	13
Females : males	7:6
Mean age, years (SD)	45.6 (12.2)
Mean weight, kg (SD)	78.48 (12.5)
Predominant race White n (%) Black n (%) Other n (%)	 9 (69.2%) 3 (23.1%) 1 (7.7%)

Primary Objective Results

The primary objective of this study is to assess the safety and tolerability of AEB071 in uveitis patients. Refer to the safety result section for safety and tolerability results.

Secondary Objective Result(s)

Table title: Summary of responder analysis

Variable	Comparison	AEB071 n/N (%)	Infliximab n/N (%)	P-value
Responders	AEB071 Total vs historical control group	4/ 13 (30.8)	16/ 22 (72.7)	0.0189
Responders	AEB071 Intermediate uveitis vs historical control group	4/ 9 (44.4)	3/ 6 (50.0)	0.6224
Responders	AEB071 Panuveitis vs historical control group	0/ 4 (0.0)	10/ 12 (83.3)	0.0082

The responders rate after treatment with AEB071 over all patients and for the subgroup of panuveitis patients observed in this study are significantly lower than the responder rates achieved with the corresponding historical Infliximab groups on the one-sided 5% level. The sub-group of Intermediate uveitis patients had a similar responder rate as the corresponding Infliximab sub-group, i.e. the responder rates were not significantly different.

Safety Results

Adverse Events by System Organ Class

Table 1 title: Adverse events (AE) overall and frequently affected system organ classes - n (%) of patients

System organ class	AEB071 N=13 n (%)*
Gastrointestinal disorders	11 (84.6)
Nervous system disorders	7 (53.8)
Skin and subcutaneous tissue disorders	3 (23.1)
Eye disorders	2 (15.4)

* Only AEs occurring in at least 10% of patients are included

Title 2: Adverse events overall and most frequent events - n (%) of patients

Preferred term	AEB071 N=13 n (%)
Subjects with AE(s)	11 (84.6)
Nausea	8 (61.5)
Diarrhea	5 (38.5)
Constipation	4 (30.8)
Dysgeusia	4 (30.8)
Vomiting	3 (23.1)
Dizziness	2 (15.4)
Dyspepsia	2 (15.4)
Headache	2 (15.4)
Retinal hemorrhage	2 (15.4)

Only AEs occurring in at least 10% of patients are included

Serious Adverse Events and Deaths

	AEB071 Treated Subjects
No. (%) of subjects studied	13
No. (%) of subjects with AE(s)	11 (84.6%)
Number (%) of subjects with serious or other significant events	n (%)
Death	0 (0%)
SAE(s)	0 (0%)
Discontinued due to SAE(s)	0 (0%)

Other Relevant Findings

Not applicable.

Date of Clinical Trial Report

To be finalized.

Date Inclusion on Novartis Clinical Trial Results Database

22 Oct 2010

Date of Latest Update

20 Oct 2010