NOVARTIS

Sponsor

Novartis

Generic Drug Name

AEB071 / Sotrastaurin

Therapeutic Area of Trial

Ulcerative colitis

Approved Indication

Investigational.

Protocol Number

CAEB071A2210

Title

A randomized, double blind, placebo controlled, parallel group design study to explore the efficacy, safety and tolerability of AEB071 in patients with active, moderate to severe ulcerative colitis

Study Phase

Phase IIb

Study Start/End Dates

20-Apr-2010 to 03-Apr-2012

Early termination date: 02-Jan-2012. Based on an interim analysis that included 47 patients the Novartis Research Decision Board decided on 02-Jan-2012 that for strategic reasons the development of AEB071 in inflammatory bowel diseases would no longer be pursued. No safety signal was observed with the interim analysis. At the time there were no patients on treatment. Study AEB071A2210 was terminated and no further patients enrolled. Investigators were informed of this decision on 13-January-2012.

Study Design/Methodology

Randomized, double-blind, placebo controlled, parallel design study of efficacy, safety and tolerability of AEB071 in 60 patients with active, moderate to severe ulcerative colitis. The patients were randomly assigned to an AEB071 300 mg/200 mg bid treatment group, or a placebo group, at a 2:1 ratio. After a 7-day screening period, patients were randomized to 2 weeks of twice-daily treatment with AEB071 300 mg or placebo followed by another 2 week twice-daily treatment with a reduced dose of AEB071 200 mg or placebo. If a patient did not tolerate the 300 mg treatment during the first 2 week treatment period, the dose level could have been adjusted to the 200 mg twice-daily level.

Centers

18 centers in 4 countries: Denmark (2), Germany (9), Poland (2), United States (5)

Publication

None

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

Oral tablets of AEB071 300 mg were administered twice daily (bid) orally for two weeks followed by 200 mg bid for an additional two weeks.

The equivalent number of matching placebo tablets (3 tablets equivalent to AEB071 300 mg) were administered orally twice daily (bid) for two weeks followed by 2 tablets (equivalent to AEB071 200 mg) bid for an additional two weeks.

Statistical Methods

The primary endpoint (clinical remission [CR] defined as a Modified Baron Score of 0 or 1 and a Partial Mayo Score of 0 or 1) and the additional endpoint (endoscopic remission [ER]) were compared between treatments using a Bayesian approach. Posterior probabilities of an improvement in response rate under AEB071 compared to placebo were calculated for the following differences:

• CR: no effect, minimal relevant effect of at least 20% difference and very promising effect of at least 50% difference

• ER: no effect, minimal relevant effect of at least 25% difference.

Sensitivity and subgroup analyses were performed to assess the robustness of primary analyses conclusions. The change from baseline in the Partial Mayo score after 4 weeks was analyzed as key secondary endpoint using a similar Bayesian approach.

Safety data, exploratory endpoints and biomarkers were summarized by treatment over time.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Male or female patients 18-75 years with an established diagnosis of moderate to severe ulcerative colitis defined as a Partial Mayo Score between 5 and 10 (inclusive), with a score of at least 2 on either stool frequency or rectal bleeding and a Modified Baron Score of at least 2 upon endoscopic examination with the disease extending at least 25 cm from the anal verge.
- Patients must have responded poorly to conventional therapy. Poor response defined as:
    - the continuous requirement for intermittent, oral steroid therapy of more than 20 mg methylprednisolone or equivalent per day for more than 3 months (including steroid dependence defined as relapse within 3 months after stopping).
    - the requirement for ≥ 2 g mesalamine per day.
    - the failure to remain symptom-free on maintenance medication of azathioprine or 6-mercaptopurin (an adequate course is considered to be at least 12 weeks of treatment).
- Female patients of childbearing potential: using two effective contraceptive methods.

Exclusion criteria

- Previous treatment with biologics (e.g. anti TNF-α) within the last 3 months or use of any other investigational drug within the previous 1 month.
- Hypersensitivity to AEB071 compound.
- Weight of less than 50 kg or more than 150 kg.
- Ongoing treatment with antibiotics, cyclosporine, methotrexate, tacrolimus or rectally administered corticosteroid or 5-aminosalicylate containing medication. Eligible patients must have stopped cyclosporine, methotrexate and tacrolimus at least 8 weeks and antibiotics and rectal topical therapy at least 2 weeks prior to study entry.
- Active or history of clinically significant cardiac abnormalities.
- Patients who are requiring the administration of strongly interacting drugs of the CYP450 3A4/5 system.
- Positive results for the detection of enteropathogens (including Salmonella, Yersinia,Shigella, Camplylobacter, EHEC and C. difficile).

Participant Flow

	AEB071 N=42	Placebo N=18	Total N=60
Patients			
Completed	34 (81.0%)	15 (83.3%)	49 (81.7%)
Discontinued	8 (19.0%)	3 (16.7%)	11 (18.3%)
Adverse Event(s)	2 (4.8%)	0 (0%)	2 (3.3%)
Lost to follow-up	1 (2.4%)	0 (0%)	1 (1.7%)
Subject withdrew consent	2 (4.8%)	1 (5.6%)	3 (5.0%)
Unsatisfactory therapeutic effect	3 (7.1%)	2 (11.1%)	5 (8.3%)

Baseline Characteristics

		AEB071 N=42	Placebo N=18	Total N=60
Age (years)	Mean (SD)	43.9 (13.8)	39.7 (13.1)	42.6 (13.6)
	Median	43.5	42.0	43.0
	Range	22 - 72	19 - 63	19 - 72
Gender - n(%)	Male	27 (64%)	11 (61%)	38 (63%)
	Female	15 (36%)	7 (39%)	22 (37%)
Predominant race - n(%)	Caucasian	40 (95%)	18 (100%)	58 (97%)
	Other	2 (5%)		2 (3%)
Ethnicity - n(%)	Other	40 (95%)	18 (100%)	58 (97%)
	Hispanic/Latino	2 (5%)		2 (3%)
Height (cm)	Mean (SD)	174.5 (10.7)	176.0 (8.4)	174.9 (10.0)
	Median	174.0	178.0	176.0
	Range	149 - 195	162 - 191	149 - 195
Weight (kg)	Mean (SD)	77.5 (13.3)	75.7 (11.5)	77.0 (12.7)
	Median	74.6	73.8	74.1
	Range	51 - 116	58 - 99	51 - 116
BMI (kg/m2)	Mean (SD)	25.6 (4.5)	24.5 (3.4)	25.2 (4.2)

		AEB071 N=42	Placebo N=18	Total N=60
	Median	25.7	24.6	25.2
	Range	17 - 35	19 - 31	17 - 35

Outcome Measures

Primary Outcome Result(s)

Bayesian analysis of clinical remission at week 4 after treatment initiation: PD analysis set

Treatment	No. responders x/n (%)	Response rate* (%)	Difference (vs Placebo) %	95% credibility interval** %	Probability (H0***) %	Probability (H1***) %	Probability (H2***) %
AEB071	6/36 (16.7)	18.4	12.2	-2.1, 27.4	95.5	14.2	0.0
Placebo	0/17 (0.0)	6.2					

* Means from the posterior Beta(1+x ,1+n-x) distribution for AEB071 and Beta(0.12*18+x, 0.88*18+n-x) distribution for placebo

** Difference in response rates simulated from the posterior probability distributions in (*)

*** H0: AEB071>pbo; H1: AEB071-placebo >=20%; H2: AEB071-placebo>=50%

Secondary Outcome Result(s)

Change in baseline in Partial Mayo score after 4 weeks: PD analysis set

Visit		AEB071 (N=37)	Placebo (N=18)
Baseline	n	37	18
	mean	7.9	8.4
	SD	1.36	1.15
	minimum	5	6
	median	8.0	9.0
	maximum	10	10
Day 8	n	37	18
	mean	5.5 (-2.4)	7.7 (-0.8)
	SD	2.36 (1.95)	1.85 (1.73)
	minimum	0 (-6)	5 (-4)
	median	6.0 (-2.0)	8.0 (-0.5)
	maximum	10 (1)	11 (2)
Day 15	n	37	18
	mean	4.6 (-3.3)	7.5 (-0.9)
	SD	2.29 (2.20)	2.48 (2.41)
	minimum	0 (-7)	3 (-6)
	median	5.0 (-4.0)	8.0 (-1.0)
	maximum	9 (0)	12 (4)
Day 22	n	37	16

	mean	4.2 (-3.7)	6.9 (-1.6)
	SD	2.78 (2.66)	2.96 (2.85)
	minimum	0 (-8)	1 (-8)
	median	4.0 (-4.0)	8.0 (0.0)
	maximum	10 (1)	10 (2)
Day 29	n	36	16
	mean	4.2 (-3.7)	6.6 (-1.9)
	SD	2.85 (2.70)	2.63 (2.66)
	minimum	0 (-8)	2 (-8)
	median	3.5 (-4.0)	7.0 (-1.0)
	maximum	10 (1)	10 (2)

Modified Baron score: PD analysis set

Treatment	Day	Range	Frequency (%)
AEB071	Baseline	Gross ulceration	9 / 37 (24.3)
		Friable mucosa	11 / 37 (29.7)
		Microulceration with spontaneous bleeding	17 / 37 (45.9)
	Day 29	Normal mucosa	2 / 36 (5.6)
		Gross ulceration	4 / 36 (11.1)
		Microulceration with spontaneous bleeding	8 / 36 (22.2)
		Friable mucosa	10 / 36 (27.8)
		Granular mucosa with an abnormal vascular pattern	12 / 36 (33.3)
Placebo	Baseline	Gross ulceration	4 / 18 (22.2)
		Friable mucosa	5 / 18 (27.8)
		Microulceration with spontaneous bleeding	9 / 18 (50)
	Day 29	Granular mucosa with an abnormal vascular pattern	2 / 15 (13.3)
		Microulceration with spontaneous bleeding	3 / 15 (20)
		Gross ulceration	4 /15 (26.7)
		Friable mucosa	6 /15 (40)

Safety Results

Adverse Events by System Organ Class

	Placebo N=18 n (%)	**AEB071 N=42 n (%)**	**Total N=60 n (%)**
Patients with AE(s)	10 (55.6%)	31 (73.8%)	41 (68.3%)
Gastrointestinal disorders	4 (22.2%)	26 (61.9%)	30 (50.0%)

	Placebo N=18 n (%)	AEB071 N=42 n (%)	Total N=60 n (%)
Renal and urinary disorders	0	12 (28.6%)	12 (20.0%)
Skin and subcutaneous tissue disorders	3 (16.7%)	9 (21.4%)	12 (20.0%)
Investigations	1 (5.6%)	8 (19.0%)	9 (15.0%)
General disorders and administration site conditions	1 (5.6%)	7 (16.7%)	8 (13.3%)
Nervous system disorders	1 (5.6%)	7 (16.7%)	8 (13.3%)
Metabolism and nutrition disorders	0	5 (11.9%)	5 (8.3%)
Infections and infestations	2 (11.1%)	2 (4.8%)	4 (6.7%)
Respiratory, thoracic and mediastinal disorders	1 (5.6%)	2 (4.8%)	3 (5.0%)
Ear and labyrinth disorders	0	2 (4.8%)	2 (3.3%)
Vascular disorders	0	2 (4.8%)	2 (3.3%)
Eye disorders	0	1 (2.4%)	1 (1.7%)
Injury, poisoning and procedural complications	1 (5.6%)	0	1 (1.7%)

AEs by SOC are presented in descending order of frequency in both treatment groups.

Most Frequently Reported AEs Overall by Preferred Term n (%)

	Placebo N=18 n (%)	AEB071 N=42 n (%)	Total N=60 n (%)
Patients with AE(s)	10 (55.6%)	31 (73.8%)	41 (68.3%)
Chromaturia	0	11 (26.2%)	11 (18.3%)
Nausea	0	11 (26.2%)	11 (18.3%)
Colitis ulcerative	1 (5.6%)	6 (14.3%)	7 (11.7%)
Dyspepsia	0	5 (11.9%)	5 (8.3%)
Fatigue	1 (5.6%)	3 (7.1%)	4 (6.7%)
Rash	0	4 (9.5%)	4 (6.7%)
Vomiting	0	4 (9.5%)	4 (6.7%)
Abdominal pain	1 (5.6%)	2 (4.8%)	3 (5.0%)
Decreased appetite	0	3 (7.1%)	3 (5.0%)
Dizziness	0	3 (7.1%)	3 (5.0%)
Eructation	1 (5.6%)	2 (4.8%)	3 (5.0%)
Headache	1 (5.6%)	2 (4.8%)	3 (5.0%)
Pyrexia	0	3 (7.1%)	3 (5.0%)
Abdominal discomfort	0	2 (4.8%)	2 (3.3%)
Acne	1 (5.6%)	1 (2.4%)	2 (3.3%)
Blood creatine phosphokinase increased	0	2 (4.8%)	2 (3.3%)
Constipation	0	2 (4.8%)	2 (3.3%)
Cough	1 (5.6%)	1 (2.4%)	2 (3.3%)

	Placebo N=18 n (%)	AEB071 N=42 n (%)	Total N=60 n (%)
Diarrhoea	0	2 (4.8%)	2 (3.3%)
Flatulence	1 (5.6%)	1 (2.4%)	2 (3.3%)
Nasopharyngitis	1 (5.6%)	1 (2.4%)	2 (3.3%)
Oral herpes	1 (5.6%)	1 (2.4%)	2 (3.3%)
Proteinuria	0	2 (4.8%)	2 (3.3%)
Skin exfoliation	1 (5.6%)	1 (2.4%)	2 (3.3%)
Urine colour abnormal	0	2 (4.8%)	2 (3.3%)
Weight decreased	0	2 (4.8%)	2 (3.3%)
Abdominal pain lower	0	1 (2.4%)	1 (1.7%)
Ageusia	0	1 (2.4%)	1 (1.7%)
Aspartate aminotransferase increased	0	1 (2.4%)	1 (1.7%)
Blister	0	1 (2.4%)	1 (1.7%)
Blood lactate dehydrogenase increased	0	1 (2.4%)	1 (1.7%)
Body temperature increased	0	1 (2.4%)	1 (1.7%)
Chills	0	1 (2.4%)	1 (1.7%)
Colitis	0	1 (2.4%)	1 (1.7%)
Concussion	1 (5.6%)	0	1 (1.7%)
Dry skin	1 (5.6%)	0	1 (1.7%)
Duodenitis	0	1 (2.4%)	1 (1.7%)
Dysgeusia	0	1 (2.4%)	1 (1.7%)
Eczema	0	1 (2.4%)	1 (1.7%)
External ear inflammation	0	1 (2.4%)	1 (1.7%)
Flushing	0	1 (2.4%)	1 (1.7%)
Gastritis haemorrhagic	0	1 (2.4%)	1 (1.7%)
Haematochezia	0	1 (2.4%)	1 (1.7%)
Haematocrit decreased	0	1 (2.4%)	1 (1.7%)
Haemoglobin decreased	0	1 (2.4%)	1 (1.7%)
Haemorrhoids	0	1 (2.4%)	1 (1.7%)
Hepatic enzyme abnormal	1 (5.6%)	0	1 (1.7%)
Hepatic enzyme increased	0	1 (2.4%)	1 (1.7%)
Hyperglycaemia	0	1 (2.4%)	1 (1.7%)
Hyperhidrosis	0	1 (2.4%)	1 (1.7%)
Hyperkalaemia	0	1 (2.4%)	1 (1.7%)
Hypertension	0	1 (2.4%)	1 (1.7%)
Intestinal obstruction	0	1 (2.4%)	1 (1.7%)

	Placebo N=18 n (%)	AEB071 N=42 n (%)	Total N=60 n (%)
Iron deficiency	0	1 (2.4%)	1 (1.7%)
Large intestinal haemorrhage	0	1 (2.4%)	1 (1.7%)
Lymphocyte count increased	0	1 (2.4%)	1 (1.7%)
Malaise	0	1 (2.4%)	1 (1.7%)
Nasal congestion	1 (5.6%)	0	1 (1.7%)
Oropharyngeal pain	0	1 (2.4%)	1 (1.7%)
Piloerection	0	1 (2.4%)	1 (1.7%)
Pruritus	0	1 (2.4%)	1 (1.7%)
Pruritus generalised	0	1 (2.4%)	1 (1.7%)
Skin hyperpigmentation	0	1 (2.4%)	1 (1.7%)
Vertigo	0	1 (2.4%)	1 (1.7%)
Visual impairment	0	1 (2.4%)	1 (1.7%)

AEs by preferred terms are presented in descending order of frequency in both treatment groups.

Serious Adverse Events and Deaths

Body system	Preferred Term	Placebo N=18 n (%)	AEB071 N=42 n (%)	Total N=60 n (%)
Any Body system		2 (11.1)	3 (7.1)	5 (8.3)
Gastrointestinal disorders	TOTAL	1 (5.6)	3 (7.1)	4 (6.7)
	Abdominal pain		1 (2.4)	1 (1.7)
	Colitis		1 (2.4)	1 (1.7)
	Colitis ulcerative	1 (5.6)	1 (2.4)	2 (3.3)
	Intestinal obstruction		1 (2.4)	1 (1.7)
Injury, poisoning and procedural complications	TOTAL	1 (5.6)		1 (1.7)
	Concussion	1 (5.6)		1 (1.7)

Other Relevant Findings

AEB071 pharmacokinetics after first dose

Parameter	AEB071	N-desmethyl-sotrastaurin
Number of patients	38	38
Tmax (h)	3.6 (1 – 8)	4 (1 – 8)
Cmax (ng/ml)	2510 ± 1050	22.6 ± 9.2
AUC(0-8h) (ng.h/ml)	13500 ± 6250	113 ± 47
Metabolic ratio	--	0.009 ± 0.002

Parameter values are mean ± sd except for Tmax which is median (range).
Metabolic ratio = metabolite/parent ratio of AUC(0-8h) in molar equivalents.

AEB071 and metabolite troughs

Visit	Dose (mg bid)	N	AEB071 C0,ss (ng/ml)	N-desmethyl-sotrastaurin C0,ss (ng/ml)
Day 2	300	35	1690 ± 1450	16.7 ± 12.4
Day 8	300	30	1010 ± 694	14.0 ± 7.8
Day 15	300	34	1110 ± 1160	14.6 ± 10.6
Day 22	200	35	663 ± 476	9.1 ± 5.4
Day 29	200	31	574 ± 383	8.0 ± 4.5

C0 values are mean ± sd.

Pharmacodynamics: predose CD3+ T-cell subset counts in ex-vivo stimulated blood samples

Dose regimen:	No drug	300 mg bid			200 mg bid	
Visit:	Day -1	Day 1	Day 2	Day 8	Day 15	Day 22	Day 29
CD69+							
Placebo	99.3 ± 0.9	99.2 ± 0.8	99.3 ± 0.6	86.4 ± 28.8	98.8 ± 0.7	99.3 ± 0.5	96.9 ± 2.4
AEB071	99.6 ± 0.3	99.3 ± 0.4	95.7 ± 2.0	97.6 ± 2.1	98.2 ± 1.4	98.7 ± 1.4	98.6 ± 1.3
IL2+							
Placebo	13.0 ± 4.6	13.4 ± 4.9	12.2 ± 5.0	9.6 ± 6.1	12.3 ± 7.4	14.6 ± 7.5	10.9 ± 7.0
AEB071	19.9 ± 13.4	25.9 ± 12.8	3.0 ± 1.8	5.5 ± 2.7	4.0 ± 2.3	6.7 ± 3.3	8.1 ± 5.4
TNFa+							
Placebo	27.1 ± 23.0	22.3 ± 16.8	24.1 ± 23.1	25.3 ± 31.6	25.9 ± 31.7	29.5 ± 34.0	29.1 ± 32.9
AEB071	30.6 ± 14.9	34.1 ± 16.8	4.6 ± 3.4	13.2 ± 12.4	9.3 ± 6.9	14.6 ± 10.5	15.4 ± 10.0
IL2/TNFa+							
Placebo	9.9 ± 4.1	9.6 ± 5.0	8.9 ± 4.8	7.9 ± 6.1	9.2 ± 6.6	11.2 ± 8.5	9.0 ± 6.3
AEB071	14.7 ± 12.0	17.0 ± 13.0	2.1 ± 1.7	4.6 ± 2.3	3.0 ± 2.0	5.5 ± 2.8	5.8 ± 3.5

Values are mean ± SD in percentage units.

Date of Clinical Trial Report

15-Mar-2013

Date Inclusion on Novartis Clinical Trial Results Database

27-Mar-2013

Date of Latest Update