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Sponsor Novartis
Generic Drug Name Sotrastaurin/AEB071
Therapeutic Area of Trial Plaque psoriasis
Approved Indication None
Protocol Number CAEB071C2201, EUDRACT no. 2007-007160-19
Title A double blind, randomized, placebo controlled, multicenter, dose finding study of oral AEB071 assessing Psoriasis Area and Severity Index (PASI) response as a function of dose (primary outcome) in patients with plaque psoriasis.
Phase of Development II
Study Start/End Dates 01-Apr-2009 (first patient first visit) 29-Aug-2011 (last patient last visit)
Study Design/Methodology This multicenter out-patient study uses a randomized, parallel-group, double blind design in patients with moderate to severe plaque psoriasis that requires systemic therapy. The study consists of 3 periods: the Screening Period, the Treatment Period of 12 weeks, and the treatment-free Follow-up Period of up to 12 weeks.
Centers Argentina (3 centers), Australia (5 centers), Austria (1 center), Belgium (4 centers), Germany (8 centers), Guatemala (3 centers), Italy (5 centers), Turkey (6 centers), United Kingdom (4 centers), United States (9 centers)
Publication None

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Outcome measures

Primary outcome measures(s)

The primary objective was to assess efficacy (as assessed by Psoriasis Area and Severity Index response [PASI]) of AEB071 in patients with moderate to severe plaque psoriasis as a function of treatment dose (50 mg BID, 100 mg OD, 100 mg BID, 200 mg OD, 200 mg BID, 300 mg BID, and 400 mg OD) after 12 weeks of treatment.

Secondary outcome measures(s)

- To evaluate overall safety of AEB071 in the Treatment and Follow-up Periods as assessed by ECG and laboratory parameters, rates of AEs, and percentage of patients requiring interruption or discontinuation of study drug due to AEs
- To evaluate the efficacy of AEB071 compared with placebo within the Treatment Period as measured by PASI and Investigator's Global Assessment (IGA)
- To evaluate the effect of treatment withdrawal and disease recurrence in the treatment-free Follow-up Period

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

Sotrastaurin 25 mg and 100 mg hard gelatin capsules for oral administration capsules

Statistical Methods

Data were analyzed according to the data analysis section 10 of the study protocol and its amendments.
An interim analysis was performed after 175 patients (approximately 50%) of the planned total number of patients had completed the treatment period of Stage 1 and data was reviewed by the data monitoring committee (DMC). Stage 2 incorporated the DMC recommendations to continue the study with the following changes: drop 50 mg BID, 100 mg OD, 100 mg BID, 200 mg OD treatment arms; and add 300 mg BID and 400 mg OD treatment arms. The final analysis of the Treatment Period was performed after all patients from both stages had completed the Treatment Period or discontinued prematurely from it. PASI 75 response at week 12 (LOCF) was modelled with a range of dose-response functions. Dose-response curves for once-daily and twice-daily dosing were fitted for Stage 1 and Stage 2 separately, enabling a model-based estimate of response for each dose together with a 95% CI. Sensitivity analyses for a per-protocol dataset and for a non-responder imputation dataset (treatment failure assumed for all missing response data at week 12, also for premature discontinuation) were performed.

The following populations were defined for analysis:

- Full analysis set

The full analysis set comprised all patients randomized to treatment. Following the intent-to-treat principle, patients were analyzed according to the treatment they were randomized to.

- Safety set

The safety set included all patients who were given at least one dose of study drug during the treatment period and had at least one post-baseline safety assessment during that period. The

statement that a patient had no AEs also constituted a safety assessment. Patients were analyzed according to treatment received at the first instance (i.e., at randomization).

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients included in this study had moderate to severe plaque psoriasis with disease severity such that systemic treatment was justified and a clinically meaningful improvement could be observed. The entry requirement of a minimum PASI score of10 and a total Body Surface Area (BSA) of minimally 10% reflected published guidelines.

Inclusion criteria

Patients meeting all of the following criteria were enrolled in the study:

1. Men and women, between 18 and 75 years of age, inclusive, at time of consent
2. Moderate to severe plaque psoriasis diagnosed for at least 12 months (with or without psoriatic arthritis as comorbidity) that required systemic therapy
3. Severity of disease meeting all of the following three criteria:
   - PASI score of 10 or greater
   - Total BSA affected by plaque psoriasis of 10% or greater
   - IGA score of 3 or greater
4. Patients able to communicate with the investigator and comply with the requirements of the study and provide written informed consent before any assessment were performed.

Exclusion criteria

Patients meeting any of the following criteria were excluded from entry into the study:

1. Hematological abnormalities i.e., leucocytes (total WBC) < 4.000/mm^3, neutrophils/granulocytes (ANC/AGC) < 1.500/mm^3, lymphocytes < 1000.000/mm^3, platelets < 100.000/mm^3, hemoglobin < 10.000 g/dL at screening
2. Heart rate < 50 or > 90 bpm when resting for 5 minutes in a sitting position
3. Family history of long QT syndrome, or QTcF > 470 msec at baseline; history of tachyarrhythmia, history of conduction abnormality; uncontrolled or unstable angina pectoris; history of myocardial infarction within the previous 12 months; known history of congestive heart failure (NYHA class II to IV) or known LVEF < 45%; history of percutaneous coronary intervention (PCI) or cardiac ablation
4. History of syncope; history of stroke or transient ischemic attack (TIA)
5. Implanted cardiac pacemaker or defibrillator
6. History of major gastrointestinal surgery (i.e., gastrectomy, gastroenterostomy, or bowel resection)
7. Evidence of being PPD+ with confirmatory chest X-ray indicating active/inactive tuberculosis at screening
8. Serum potassium level outside normal range
9. Known to be immunocompromised or positive human immunodeficiency virus (HIV) test result at screening; positive hepatitis B (HBsAg) or hepatitis C (anti-HCV) test result at screening
10. Abnormalities in liver function tests i.e., AST or ALT ≥ 3.0 x upper limits of normal

(ULN), and/or total bilirubin ≥ 1.5 x ULN

11. Active systemic infections within the past 2 weeks other than common cold
12. History of malignancy of any organ system, treated or untreated, whether or not there is evidence of local recurrence or metastases
13. Current guttate, generalized erythrodermic, or pustular psoriasis (symptoms of inverse psoriasis are allowed as long as plaque psoriasis is predominant)
14. Current drug associated psoriasis, i.e., new onset or exacerbation of psoriasis from e.g., beta-blockers, ACE inhibitors, or angiotensin receptor blockers
15. History of drug or alcohol abuse within the 12 months prior to screening
16. Hypersensitivity to sotrastaurin or any ingredient of study drug
17. Any significant medical condition the severity of which prevents the patient from participating in this study according to investigators assessment
18. Use of prohibited treatments/medications within the period specified or planned use of these prohibited treatments/medications during the study.
19. Body weight below 45 kg
20. Donation or loss of 400 mL or more blood within 8 weeks prior to first dosing, or longer if required by local regulation
21. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL)
22. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless using an approved form of contraception

No additional exclusions could be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

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Sotrastaurin within the tables presented below is referred to as AEB071.

Participant Flow

Patient disposition in treatment period, by treatment (Full analysis set)

	Treatments continued or new in Stage 2				Treatments not continued into Stage 2			
	AEB071 200 mg BID n (%)	AEB071 400 mg OD n (%)	AEB071 300 mg BID n (%)	Placebo n (%)	AEB071 50 mg BID n (%)	AEB071 100 mg OD n (%)	AEB071 100 mg BID n (%)	AEB071 200 mg OD n (%)
Randomized	56 (100)	52 (100)	53 (100)	60 (100)	29 (100)	31 (100)	31 (100)	27 (100)
Exposed	56 (100)	52 (100)	53 (100)	60 (100)	29 (100)	31 (100)	30 (96.8)	27 (100)
Treatment period								
Completed	39 (69.6)	34 (65.4)	44 (83.0)	36 (60.0)	27 (93.1)	25 (80.6)	20 (64.5)	23 (85.2)
Discontinued	17 (30.4)	18 (34.6)	9 (17.0)	24 (40.0)	2 (6.9)	6 (19.4)	11 (35.5)	4 (14.8)
Primary reason for discontinuation								
Adverse Event(s)	9 (16.1)	10 (19.2)	3 (5.7)	7 (11.7)	0 (0.0)	2 (6.5)	3 (9.7)	1 (3.7)
Unsatis. ther. effect	4 (7.1)	2 (3.8)	2 (3.8)	14 (23.3)	2 (6.9)	3 (9.7)	2 (6.5)	2 (7.4)
Subj. withdrew consent	1 (1.8)	4 (7.7)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (9.7)	1 (3.7)
Abnormal test result(s)	2 (3.6)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Administrat. problems	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)
Subj. cond. no longer requires study drug	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)
Protocol deviation	1 (1.8)	1 (1.9)	0 (0.0)	1 (1.7)	0 (0.0)	1 (3.2)	1 (3.2)	0 (0.0)
Follow-up period								
Did not enter follow-up [a]	6 (10.7)	7 (13.5)	6 (11.3)	10 (16.7)	9 (31.0)	10 (32.3)	3 (9.7)	6 (22.2)
Entered follow-up [b]	37 (66.1)	30 (57.7)	40 (75.5)	29 (48.3)	18 (62.1)	16 (51.6)	17 (54.8)	17 (63.0)
Completed	22 (39.3)	16 (30.8)	20 (37.7)	22 (36.7)	11 (37.9)	8 (25.8)	8 (25.8)	9 (33.3)
Discontinued	15 (26.8)	14 (26.9)	20 (37.7)	7 (11.7)	7 (24.1)	8 (25.8)	9 (29.0)	8 (29.6)
Primary reason for discontinuation/not entering follow-up [a]								
Unsatisfactory. therapeutic. effect	10 (17.9)	9 (17.3)	15 (28.3)	14 (23.3)	11 (37.9)	14 (45.2)	5 (16.1)	9 (33.3)
Subj. withdrew consent	6 (10.7)	1 (1.9)	5 (9.4)	2 (3.3)	2 (6.9)	0 (0.0)	1 (3.2)	1 (3.7)
Adverse Event(s)	5 (8.9)	9 (17.3)	3 (5.7)	1 (1.7)	2 (6.9)	4 (12.9)	6 (19.4)	4 (14.8)
Protocol deviation	0 (0.0)	0 (0.0)	2 (3.8)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	2 (3.8)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Baseline Characteristics

Demographic summary (Full analysis set - Treatments continued or new in Stage 2)

	AEB071 200 mg BID N=56	AEB071 400 mg OD N=52	AEB071 300 mg BID N=53	Placebo N=60
Age (years)				
n	56	52	53	60
Mean	42.5	38.6	42.6	43.9
SD	13.25	11.56	13.12	11.86
Median	41.0	38.0	40.0	44.0

Min - Max	19 - 73	19 - 68	21 - 71	21 - 73
Age group - n (%)				
18 - 44 years	31 (55.4)	39 (75.0)	30 (56.6)	31 (51.7)
45 - 64 years	21 (37.5)	12 (23.1)	19 (35.8)	27 (45.0)
>= 65 years	4 (7.1)	1 (1.9)	4 (7.5)	2 (3.3)
Sex - n (%)				
Male	40 (71.4)	38 (73.1)	38 (71.7)	38 (63.3)
Female	16 (28.6)	14 (26.9)	15 (28.3)	22 (36.7)
Race - n (%)				
Caucasian	42 (75.0)	44 (84.6)	45 (84.9)	45 (75.0)
Black	2 (3.6)	0 (0.0)	0 (0.0)	2 (3.3)
Asian	3 (5.4)	2 (3.8)	1 (1.9)	1 (1.7)
Native American	1 (1.8)	0 (0.0)	0 (0.0)	2 (3.3)
Other	8 (14.3)	6 (11.5)	7 (13.2)	10 (16.7)
Weight (kg) at baseline				
n	56	52	53	60
Mean	89.5	85.3	91.2	87.1
SD	22.44	19.89	23.37	24.88
Median	87.5	81.0	86.5	83.8
Min - Max	49.4 - 144.0	48.0 - 131.0	50.0 - 170.9	45.0 - 193.0
Height (cm)				
n	56	52	53	60
Mean	171	172	172	170
SD	8.7	9.2	11.9	9.7
Median	172	175	174	170
Min - Max	151 - 189	151 - 188	150 - 193	148 - 186
BMI (kg/m^2) at baseline				
n	56	52	53	60
Mean	30.4	28.7	30.7	29.7
SD	6.77	6.29	7.27	6.96
Median	29.2	27.9	29.1	28.3
Min - Max	17.1 - 47.1	17.3 - 49.6	19.5 - 49.9	18.7 - 59.6
BMI group (kg/m^2) - n (%)				
Underweight (< 18.5)	1 (1.8)	1 (1.9)	0 (0.0)	0 (0.0)
Normal (18.5 - < 25.0)	11 (19.6)	15 (28.8)	15 (28.3)	15 (25.0)
Overweight (25.0 - < 30)	18 (32.1)	16 (30.8)	13 (24.5)	23 (38.3)
Obese (>= 30.0)	26 (46.4)	20 (38.5)	25 (47.2)	22 (36.7)

BMI = Body mass index (= weight [kg] / height [m^2]). Baseline = Visit 3.

Stage 1: The treatment groups were comparable in terms of the baseline demographic characteristics

Baseline disease characteristics (Full analysis set - Treatments continued or new in Stage 2)

	AEB071 200 mg BID N=56	**AEB071 400 mg OD N=52**	**AEB071 300 mg BID N=53**	**Placebo N=60**
Time since first diagnosis of psoriasis (yrs)				
n	56	52	52	60

Mean	14.5	14.5	15.9	18.1
SD	9.82	11.75	10.00	10.48
Median	12.6	10.6	15.6	19.0
Min - Max	1.4 - 43.0	1.5 - 42.5	1.1 - 44.5	1.5 - 45.5
Current involvement of - n (%)				
Palms	8 (14.3)	8 (15.4)	6 (11.3)	5 (8.3)
Soles	8 (14.3)	6 (11.5)	6 (11.3)	8 (13.3)
Face	18 (32.1)	23 (44.2)	19 (35.8)	31 (51.7)
Genitals	16 (28.6)	14 (26.9)	15 (28.3)	15 (25.0)
Last type of therapy - n (%)				
Systemic	18 (32.1)	26 (50.0)	21 (39.6)	25 (41.7)
UV	12 (21.4)	9 (17.3)	10 (18.9)	8 (13.3)
Topical	41 (73.2)	41 (78.8)	37 (69.8)	46 (76.7)
Psoriatic arthritis comorbidity - n (%)				
No	51 (91.1)	51 (98.1)	48 (90.6)	56 (93.3)
Yes	5 (8.9)	1 (1.9)	5 (9.4)	4 (6.7)
Total BSA affected by plaque psoriasis (%)				
n	56	52	53	60
Mean	27.7	30.4	29.2	28.0
SD	14.92	15.88	16.12	14.70
Median	24.4	27.2	23.1	27.0
Min - Max	6.5 - 69.0	9.2 - 74.5	10.6 - 73.5	1.7 - 73.0
PASI score				
n	56	52	53	60
Mean	19.3	22.2	20.1	19.2
SD	7.91	10.94	9.48	7.50
Median	17.4	18.7	17.3	17.5
Min - Max	10.6 - 41.0	10.0 - 55.8	10.4 - 55.8	6.9 - 37.8
Investigator's Global Assessment (IGA) - n (%)				
0 - Clear	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 - Almost clear	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2 - Mild disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3 - Moderate disease	33 (58.9)	26 (50.0)	28 (52.8)	35 (58.3)
4 - Severe disease	18 (32.1)	22 (42.3)	22 (41.5)	22 (36.7)
5 - Very severe disease	5 (8.9)	4 (7.7)	3 (5.7)	3 (5.0)

Stage 1: : The enrolled patient population reflected a typical patient population usually enrolled in phase 3 clinical trial in moderate to severe psoriasis

Outcome measures

Due to limited efficacy, Stage 1 efficacy data is not being presented, except for the primary endpoint.

Primary Outcome Result(s)

Primary analysis results of PASI 75: Estimated probability of PASI75 response by dose at Week 12 (LOCF) (Full analysis set)

Treatment	n	Number (%) of patients with PASI75	Estimate (%)	95% CI (%)

AEB071 50 mg BID	29	5 (17.2)	11.2	(5.4, 17.4)
AEB071 100 mg OD	31	3 (9.7)	12.2	(6.4, 19.7)
AEB071 100 mg BID	31	3 (9.7)	14.3	(7.3, 22.3)
AEB071 200 mg OD	27	6 (22.2)	22.3	(11.1, 37.0)
AEB071 200 mg BID (total)	56	15 (26.8)	25.4	(13.1, 35.5)
AEB071 200 mg BID (Stage 1)	28	10 (35.7)	35.1	(20.2, 51.2)
AEB071 200 mg BID (Stage 2)	28	5 (17.9)	17.9	(5.7, 30.9)
AEB071 400 mg OD	52	17 (32.7)	32.0	(20.1, 44.4)
AEB071 300 mg BID	53	27 (50.9)	49.3	(36.0, 63.7)
Placebo (total)	60	4 (6.7)	5.5	(1.2, 11.0)
Placebo (Stage 1)	29	3 (10.3)	9.3	(2.9, 16.7)
Placebo (Stage 2)	31	1 (3.2)	3.4	(0.3, 8.7)

Estimates are based on the bootstrap method. 1000 bootstrap samples are used.

n = number of patients where PASI 75 was assessed.

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Secondary Outcome Result(s)

Analysis of percentage change from baseline in PASI score, by treatment period visit (Full analysis set - Treatments continued or new in Stage 2)

					Difference to placebo (AEB071 - placebo)			
Visit	Treatment	n	LS Mean	SE	LS Mean	SE	95% CI	p-value
Week 1	AEB071 200 mg BID	53	-22.0	3.04	-18.6	3.62	(-25.7, -11.4)	<.001
	AEB071 400 mg OD	46	-21.0	3.79	-17.6	4.13	(-25.7, -9.5)	<.001
	AEB071 300 mg BID	52	-22.2	3.52	-18.7	4.01	(-26.6, -10.9)	<.001
	Placebo	59	-3.4	2.96	-	-	-	-
Week 2	AEB071 200 mg BID	50	-38.9	3.58	-34.9	4.43	(-43.7, -26.2)	<.001
	AEB071 400 mg OD	45	-39.9	4.26	-35.9	4.89	(-45.5, -26.3)	<.001
	AEB071 300 mg BID	51	-41.3	3.98	-37.3	4.74	(-46.6, -28.0)	<.001
	Placebo	58	-4.0	3.43				
Week 4	AEB071 200 mg BID	50	-50.9	4.09	-40.7	5.28	(-51.0, -30.3)	<.001
	AEB071 400 mg OD	44	-51.4	4.75	-41.1	5.71	(-52.3, -29.9)	<.001
	AEB071 300 mg BID	51	-59.1	4.43	-48.8	5.53	(-59.7, -37.9)	<.001
	Placebo	49	-10.3	4.01	-	-	-	-
Week 6	AEB071 200 mg BID	42	-55.4	4.60	-45.5	6.13	(-57.5, -33.4)	<.001
	AEB071 400 mg OD	41	-58.9	5.20	-48.9	6.51	(-61.7, -36.1)	<.001
	AEB071 300 mg BID	49	-66.2	4.83	-56.3	6.29	(-68.6, -43.9)	<.001
	Placebo	40	-10.0	4.61				
Week 8	AEB071 200 mg BID	42	-54.3	5.03	-43.6	6.83	(-57.0, -30.1)	<.001
	AEB071 400 mg OD	40	-57.4	5.60	-46.7	7.20	(-60.8, -32.5)	<.001
	AEB071 300 mg BID	48	-67.9	5.18	-57.2	6.94	(-70.9, -43.6)	<.001
	Placebo	37	-10.7	5.13	-	-	-	-
Week 10	AEB071 200 mg BID	40	-49.8	5.36	-33.8	7.34	(-48.3, -19.3)	<.001
	AEB071 400 mg OD	35	-54.7	5.96	-38.6	7.72	(-53.8, -23.4)	<.001
	AEB071 300 mg BID	45	-68.9	5.46	-52.9	7.41	(-67.4, -38.3)	<.001
	Placebo	37	-16.0	5.48				
Week 12	AEB071 200 mg BID	39	-52.6	5.73	-35.0	7.91	(-50.6, -19.4)	<.001
	AEB071 400 mg OD	34	-52.7	6.35	-35.0	8.30	(-51.4, -18.7)	<.001
	AEB071 300 mg BID	44	-65.3	5.78	-47.7	7.94	(-63.3, -32.0)	<.001
	Placebo	36	-17.6	5.88	-	-	-	-

LS Mean = least squares mean, SE = standard error of the mean, CI = confidence interval.

Analysis of covariance repeated measures model: Perc. change of PASI = treatment + baseline PASI + region + study stage + baseline weight + psoriatic arthritis comorbidity + visit + treatment x visit + error.

Perc. change = 100 x (post baseline – baseline) / baseline

Investigator's Global Assessment (IGA), by treatment period visit (Full analysis set - Treatments continued or new in Stage 2)

Visit	Statistic	**AEB071 200 mg BID N=56**	**AEB071 400 mg OD N=52**	**AEB071 300 mg BID N=53**	**Placebo N=60**
Week 1	n evaluable	53	46	52	59
	Success, n (%)	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)

Week 2	n evaluable	50	45	51	58
	Success, n (%)	2 (4.0)	3 (6.7)	0 (0.0)	0 (0.0)
Week 4	n evaluable	50	44	51	49
	Success, n (%)	5 (10.0)	7 (15.9)	8 (15.7)	0 (0.0)
Week 6	n evaluable	42	41	49	40
	Success, n (%)	4 (9.5)	9 (22.0)	16 (32.7)	0 (0.0)
Week 8	n evaluable	42	40	48	37
	Success, n (%)	5 (11.9)	8 (20.0)	21 (43.8)	0 (0.0)
Week 10	n evaluable	40	35	45	37
	Success, n (%)	8 (20.0)	10 (28.6)	20 (44.4)	0 (0.0)
Week 12	n evaluable	39	34	44	36
	Success, n (%)	10 (25.6)	9 (26.5)	17 (38.6)	0 (0.0)
Week 12 (LOCF)	n evaluable	56	52	53	60
	Success, n (%)	12 (21.4)	10 (19.2)	19 (35.8)	0 (0.0)

Treatment success = IGA score of 0 (clear) or 1 (almost clear) and at least 2 grade improvement.

LOCF = Last observation carried forward (which included the baseline value, i.e., patients with no post baseline data were treated as failure).

The planned logistic regression model was not practicable since there was no patient in the placebo group with treatment success at any visit.

Relapse, time to relapse, loss of PASI 75, and time to loss of PASI 75 during the follow-up period (Full analysis set - Treatments continued or new in Stage 2)

	AEB071 200 mg BID N=56	**AEB071 400 mg OD N=52**	**AEB071 300 mg BID N=53**	**Placebo N=60**
Relapse (first definition)				
Patients evaluable	11	14	25	4
n (%) with relapse	4 (36.4)	6 (42.9)	10 (40.0)	1 (25.0)
Time to relapse (first definition)				
Median (days)	92.0	89.0	n.e.	n.e.
95% CI of the median	(54.0,n.e.)	(84.0,n.e.)	(50.0,n.e.)	(57.0,n.e.)
p-value of log-rank test vs. placebo	0.787	0.552	0.390	
Relapse (second definition)				
Patients evaluable	17	17	29	4
n (%) with relapse	7 (41.2)	11 (64.7)	15 (51.7)	1 (25.0)
Time to relapse (second definition)				
Median (days)	92.0	88.0	60.0	n.e.
95% CI of the median	(54.0,n.e.)	(35.0,89.0)	(35.0,n.e.)	(57.0,n.e.)
p-value of log-rank test vs. placebo	0.581	0.242	0.236	
Loss of PASI 75				
Patients evaluable	11	14	25	4
n (%) with loss of PASI 75	6 (54.5)	11 (78.6)	20 (80.0)	3 (75.0)
Time to loss of PASI 75				
Median (days)	92.0	45.0	29.0	48.5
95% CI of the median	(54.0,n.e.)	(28.0,84.0)	(28.0,53.0)	(28.0,n.e.)
p-value of log-rank test vs. placebo	0.394	0.699	0.489	

Relapse (first definition) = a worsening > 50% of the PASI improvement achieved at the end of treatment. To be evaluable, patients had to be responders (PASI 75) at end of treatment and participate in the follow-up period. Relapse (second definition) = a worsening > 50% of the maximum PASI improvement achieved during the treatment period. To be evaluable, patients had to be responders (PASI 75) on at least one treatment period visit and participate in the follow-up period. To be evaluable for loss of PASI 75, patients had to be responders (PASI 75) at end of treatment and participate in the follow-up period.

Time to relapse/loss of PASI 75 was calculated from start of follow-up period up to the day of first relapse/loss of PASI 75. Patients without a relapse/loss of PASI 75 were considered as censored at the last follow-up period visit with PASI assessments.

Median time to relapse/loss of PASI 75 was calculated by the Kaplan Meier method.

CI = confidence interval, n.e. = not estimable

Rebound and time to rebound during the follow-up period (Full analysis set - Treatments continued or new in Stage 2)

	AEB071 200 mg BID N=56	AEB071 400 mg OD N=52	AEB071 300 mg BID N=53	Placebo N=60
Rebound (first definition)				
Patients evaluable	36	30	40	29
n (%) with rebound	6 (16.7)	2 (6.7)	1 (2.5)	3 (10.3)
Time to rebound (first definition)				
Median (days)	n.e.	n.e.	n.e.	n.e.
95% CI of the median	(n.e.,n.e.)	(n.e.,n.e.)	(n.e.,n.e.)	(n.e.,n.e.)
p-value of log-rank test vs. placebo	0.375	0.773	0.328	
Rebound (second definition)				
Patients evaluable	11	14	25	4
n (%) with rebound	1 (9.1)	1 (7.1)	0 (0.0)	0 (0.0)
Time to rebound (second definition)				
Median (days)	n.e.	n.e.	n.e.	n.e.
95% CI of the median	(n.e.,n.e.)	(n.e.,n.e.)	(n.e.,n.e.)	(n.e.,n.e.)
p-value of log-rank test vs. placebo	0.546	0.579	n.e.	

Rebound = PASI increased to >= 125% of baseline PASI, or new pustular or erythrodermic psoriasis occurred, within 3 months after the study drug had been discontinued.

To be evaluable for the first definition, patients had to participate in the follow-up period.

To be evaluable for the second definition, patients had to be responders (PASI 75) at the end of treatment and had to participate in the follow-up period.

Time to rebound was calculated from start of follow-up period up to the first follow-up visit where rebound was reported. Patients without a rebound were considered as censored at the last follow-up period visit with rebound assessments.

Median time to rebound was calculated by the Kaplan Meier method.

CI = confidence interval, n.e. = not estimable.

The percentage of patients with loss of PASI 75 or relapse, seem to be higher in the 300 mg BID dose group and lower in the lower dose groups and placebo group, probably reflecting a selection bias, as it is likely that responders with lower doses, or placebo presented with a psoriasis probably less challenging to treat.

Rebound was observed more in the dose groups that were less effective (2 patients experienced a rebound (any patient who had achieved PASI 75 response at Week 12 and presented during follow-up period an increased PASI >= 125% of baseline, or new or erythrodermic psoriasis); one each in the AEB071 200 mg BID and 400 mg OD groups.

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Safety Results

Adverse Events by System Organ Class

Adverse events during treatment period, by primary system organ class - n (%) of patients (Safety set - Treatments continued or new in Stage 2)

	AEB071 200 mg BID N=57 n (%)	AEB071 400 mg OD N=51 n (%)	AEB071 300 mg BID N=53 n (%)	Placebo N=59 n (%)
Patients with any AE(s)	51 (89.5)	49 (96.1)	50 (94.3)	48 (81.4)
Primary system organ class				
Gastrointestinal disorders	30 (52.6)	40 (78.4)	40 (75.5)	23 (39.0)
Nervous system disorders	27 (47.4)	26 (51.0)	24 (45.3)	22 (37.3)
Infections and infestations	16 (28.1)	21 (41.2)	17 (32.1)	13 (22.0)
Skin and subcutaneous tissue disorders	18 (31.6)	17 (33.3)	17 (32.1)	22 (37.3)
Cardiac disorders	11 (19.3)	7 (13.7)	11 (20.8)	3 (5.1)
Investigations	13 (22.8)	6 (11.8)	11 (20.8)	5 (8.5)
Musculoskeletal and connective tissue disorders	8 (14.0)	5 (9.8)	10 (18.9)	14 (23.7)
General disorders and administration site conditions	9 (15.8)	6 (11.8)	8 (15.1)	5 (8.5)
Respiratory, thoracic and mediastinal disorders	3 (5.3)	6 (11.8)	7 (13.2)	8 (13.6)
Metabolism and nutrition disorders	4 (7.0)	5 (9.8)	4 (7.5)	4 (6.8)
Psychiatric disorders	3 (5.3)	0 (0.0)	3 (5.7)	3 (5.1)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	2 (3.8)	2 (3.4)
Blood and lymphatic system disorders	1 (1.8)	1 (2.0)	1 (1.9)	0 (0.0)
Ear and labyrinth disorders	2 (3.5)	0 (0.0)	1 (1.9)	1 (1.7)
Eye disorders	1 (1.8)	0 (0.0)	1 (1.9)	2 (3.4)
Injury, poisoning and procedural complications	1 (1.8)	0 (0.0)	1 (1.9)	2 (3.4)
Vascular disorders	1 (1.8)	3 (5.9)	1 (1.9)	0 (0.0)
Immune system disorders	4 (7.0)	1 (2.0)	0 (0.0)	2 (3.4)
Renal and urinary disorders	0 (0.0)	2 (3.9)	0 (0.0)	0 (0.0)

Primary system organ classes are sorted in descending order of frequency in the AEB071 300 mg BID group.

Adverse events starting in the follow-up period, by primary system organ class - n (%) of patients (Safety set - Treatments continued or new in Stage 2)

	AEB071 200 mg BID N=38 n (%)	AEB071 400 mg OD N=29 n (%)	AEB071 300 mg BID N=40 n (%)	Placebo N=28 n (%)
Patients with any AE(s)	15 (39.5)	13 (44.8)	13 (32.5)	14 (50.0)
Primary system organ class				
Skin and subcutaneous tissue disorders	8 (21.1)	6 (20.7)	6 (15.0)	1 (3.6)
Nervous system disorders	1 (2.6)	0 (0.0)	4 (10.0)	1 (3.6)
Musculoskeletal and connective tissue disorders	2 (5.3)	1 (3.4)	3 (7.5)	3 (10.7)
Infections and infestations	2 (5.3)	5 (17.2)	2 (5.0)	7 (25.0)
Respiratory, thoracic and mediastinal disorders	1 (2.6)	0 (0.0)	2 (5.0)	1 (3.6)
Eye disorders	1 (2.6)	0 (0.0)	1 (2.5)	0 (0.0)

Gastrointestinal disorders	1 (2.6)	0 (0.0)	1 (2.5)	3 (10.7)
Injury, poisoning and procedural complications	1 (2.6)	1 (3.4)	1 (2.5)	1 (3.6)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)
Psychiatric disorders	2 (5.3)	0 (0.0)	1 (2.5)	0 (0.0)
Cardiac disorders	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital, familial and genetic disorders	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)

Starting in the follow-up period means more than 7 days after end of treatment.
Primary system organ classes are sorted in descending order of frequency in the AEB071 300 mg BID group.

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

Most frequent adverse events during treatment period (> 5.0 % in any treatment group), by preferred term - n (%) of patients (Safety set - Treatments continued or new in Stage 2)

	AEB071 200 mg BID N=57 n (%)	AEB071 400 mg OD N=51 n (%)	AEB071 300 mg BID N=53 n (%)	Placebo N=59 n (%)
Patients with any AE(s)	51 (89.5)	49 (96.1)	50 (94.3)	48 (81.4)
Preferred term				
Diarrhea	14 (24.6)	29 (56.9)	24 (45.3)	10 (16.9)
Nausea	14 (24.6)	24 (47.1)	23 (43.4)	6 (10.2)
Headache	22 (38.6)	19 (37.3)	17 (32.1)	20 (33.9)
Vomiting	4 (7.0)	10 (19.6)	10 (18.9)	2 (3.4)
Constipation	9 (15.8)	7 (13.7)	8 (15.1)	1 (1.7)
Dysgeusia	4 (7.0)	5 (9.8)	6 (11.3)	2 (3.4)
Sinus tachycardia	1 (1.8)	2 (3.9)	6 (11.3)	0 (0.0)
Abdominal pain	5 (8.8)	4 (7.8)	5 (9.4)	2 (3.4)
Back pain	4 (7.0)	2 (3.9)	5 (9.4)	3 (5.1)
Cough	0 (0.0)	4 (7.8)	5 (9.4)	4 (6.8)
Influenza	0 (0.0)	3 (5.9)	5 (9.4)	1 (1.7)
Psoriasis	4 (7.0)	6 (11.8)	5 (9.4)	10 (16.9)
Abdominal discomfort	2 (3.5)	2 (3.9)	4 (7.5)	0 (0.0)
Abdominal pain upper	4 (7.0)	4 (7.8)	4 (7.5)	2 (3.4)
Blood creatine phosphokinase increased	4 (7.0)	0 (0.0)	4 (7.5)	2 (3.4)
Dizziness	3 (5.3)	6 (11.8)	4 (7.5)	1 (1.7)
Pruritus	4 (7.0)	3 (5.9)	4 (7.5)	6 (10.2)
Abdominal distension	2 (3.5)	3 (5.9)	3 (5.7)	0 (0.0)
Arthralgia	3 (5.3)	1 (2.0)	3 (5.7)	6 (10.2)
Asthenia	4 (7.0)	0 (0.0)	3 (5.7)	0 (0.0)
Decreased appetite	2 (3.5)	1 (2.0)	3 (5.7)	0 (0.0)
Eczema	0 (0.0)	1 (2.0)	3 (5.7)	0 (0.0)
Gastrooesophageal reflux disease	0 (0.0)	2 (3.9)	3 (5.7)	0 (0.0)
Oropharyngeal pain	3 (5.3)	3 (5.9)	3 (5.7)	4 (6.8)

Upper respiratory tract infection	3 (5.3)	2 (3.9)	3 (5.7)	4 (6.8)
Dyspepsia	3 (5.3)	4 (7.8)	2 (3.8)	3 (5.1)
Electrocardiogram T wave amplitude decreased	1 (1.8)	4 (7.8)	2 (3.8)	1 (1.7)
Fatigue	1 (1.8)	3 (5.9)	2 (3.8)	2 (3.4)
Nasopharyngitis	6 (10.5)	7 (13.7)	2 (3.8)	1 (1.7)
Toothache	2 (3.5)	0 (0.0)	2 (3.8)	4 (6.8)
Urinary tract infection	1 (1.8)	3 (5.9)	2 (3.8)	1 (1.7)
Atrioventricular block first degree	3 (5.3)	1 (2.0)	1 (1.9)	1 (1.7)
Hypertriglyceridaemia	0 (0.0)	2 (3.9)	1 (1.9)	4 (6.8)
Pruritus generalised	6 (10.5)	1 (2.0)	1 (1.9)	3 (5.1)
Anxiety	3 (5.3)	0 (0.0)	0 (0.0)	1 (1.7)
Flatulence	2 (3.5)	3 (5.9)	0 (0.0)	0 (0.0)
Seasonal allergy	3 (5.3)	1 (2.0)	0 (0.0)	2 (3.4)

Preferred terms are sorted in descending order of frequency in the AEB071 300 mg BID group.

Most frequent adverse events starting in the follow-up period (>= 5.0 % in any treatment group), by preferred term - n (%) of patients (Safety set - Treatments continued or new in Stage 2)

	AEB071 200 mg BID N=38 n (%)	AEB071 400 mg OD N=29 n (%)	AEB071 300 mg BID N=40 n (%)	Placebo N=28 n (%)
Patients with any AE(s)	15 (39.5)	13 (44.8)	13 (32.5)	14 (50.0)
Preferred term				
Headache	1 (2.6)	0 (0.0)	3 (7.5)	1 (3.6)
Psoriasis	2 (5.3)	4 (13.8)	3 (7.5)	0 (0.0)
Arthralgia	0 (0.0)	0 (0.0)	2 (5.0)	2 (7.1)
Nasopharyngitis	0 (0.0)	2 (6.9)	2 (5.0)	2 (7.1)
Pruritus	2 (5.3)	1 (3.4)	1 (2.5)	1 (3.6)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.1)

Starting in the follow-up period means more than 7 days after end of treatment.
Preferred terms are sorted in descending order of frequency in the AEB071 300 mg BID group.

Stage 1: In the treatment period, the overall incidence of AEs was the highest in the AEB071 100 mg OD group (31/32, 96.9%) and the lowest in the AEB071 50 mg BID and 100 mg BID groups (26/29, 89.7%). The most commonly affected primary SOCs were gastrointestinal disorders, nervous system disorders, infections and infestations, and skin and subcutaneous tissue disorders.

In the follow-up period, the overall incidence of AEs was the highest in the patients that had received AEB071 100 mg BID (8/17, 47.1%). The most commonly affected primary SOCs were skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders and infections and infestations.

Serious Adverse Events and Deaths

Deaths and other serious adverse events during treatment period and adverse events

leading to permanent discontinuation of study drug – n (%) of patients (Safety set)

	Treatments continued or new in Stage 2			
	AEB071 200 mg BID N=57 n (%)	**AEB071 400 mg OD N=51 n (%)**	**AEB071 300 mg BID N=53 n (%)**	**Placebo N=59 n (%)**
Patients with any AE(s)	51 (89.5)	49 (96.1)	50 (94.3)	48 (81.4)
Serious AEs or AE discontinuations				
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAE(s)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to AE(s)	10 (17.5)	10 (19.6)	3 (5.7)	8 (13.6)
Discontinued due to SAE(s)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to non-SAE(s)	9 (15.8)	10 (19.6)	3 (5.7)	8 (13.6)
	Treatments not continued into Stage 2			
	AEB071 50 mg BID N=29 n (%)	**AEB071 100 mg OD N=32 n (%)**	**AEB071 100 mg BID N=29 n (%)**	**AEB071 200 mg OD N=28 n (%)**
Patients with any AE(s)	26 (89.7)	31 (96.9)	26 (89.7)	26 (92.9)
Serious AEs or AE discontinuations				
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAE(s)	0 (0.0)	1 (3.1)	0 (0.0)	1 (3.6)
Discontinued due to AE(s)	0 (0.0)	2 (6.3)	3 (10.3)	2 (7.1)
Discontinued due to SAE(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to non-SAE(s)	0 (0.0)	2 (6.3)	3 (10.3)	2 (7.1)

A patient could have discontinued study treatment due to both a SAE and a non-SAE

Serious adverse events during treatment period, by preferred term - n (%) of patients (Safety set - Treatments continued or new in Stage 2)

	AEB071 200 mg BID N=57 n (%)	**AEB071 400 mg OD N=51 n (%)**	**AEB071 300 mg BID N=53 n (%)**	**Placebo N=59 n (%)**
Preferred term				
Rebound psoriasis	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)

Preferred terms are sorted in descending order of frequency in the AEB071 300 mg BID group.

Stage 1: Two SAEs (gastroenteritis and cholecystitis acute) were reported in the AEB071 100 mg OD and the AEB071 200 mg OD groups, respectively. No discontinuations due to AEs were reported in the AEB071 50 mg BID group. Across the other treatment groups, discontinuations due AEs were higher in the AEB071 100 mg BID group (3/29, 10.3%) as compared to the AEB071 100 mg OD (2/32, 6.3%) and AEB071 200 mg OD groups (2/28, 7.1%). No SAEs were reported in the follow-up period.

Other Relevant Findings

Vital Signs

Number (%) of patients with clinically notable vital signs values at any time during treatment period (Safety set - Treatments continued or new in Stage 2)

	AEB071 200 mg BID N=57 n (%)	AEB071 400 mg OD N=51 n (%)	AEB071 300 mg BID N=53 n (%)	Placebo N=59 n (%)
Systolic blood pressure (mm Hg)				
>= 140 mm Hg	17 (29.8)	22 (44.0)	16 (30.2)	14 (24.1)
< 90 mm Hg	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Diastolic blood pressure (mm Hg)				
>= 90 mm Hg	20 (35.1)	17 (34.0)	22 (41.5)	12 (20.7)
< 60 mm Hg	2 (3.5)	4 (8.0)	4 (7.5)	3 (5.2)
Pulse rate (bpm)				
> 100 bpm	3 (5.3)	0 (0.0)	4 (7.5)	0 (0.0)
< 60 bpm	6 (10.5)	4 (8.0)	6 (11.3)	8 (13.8)

Stage 1: Similar number of patients in the AEB071 50 mg BID group (13 patients); AEB071 100 mg OD group (15 patients); AEB071 100 mg BID group (11 patients including apatient who had hypertension reported as an AE; which was continuing) and AEB071 200 mg OD group (9 patients) reported systolic blood pressure ≥140 mmHg.

Similar number of patients in the AEB071 50 mg BID group (12 patients); AEB071 100 mg OD group (13 patients); AEB071 100 mg BID group (9 patients including a patient who had tachycardia reported as an AE starting on Day 22 and considered resolved on Day 25) and AEB071 200 mg OD group (12 patients including a patient who had AEs of biphasic T waves, depressed ST segment, inverted T waves and flat T waves reported which were ongoing) reported diastolic blood pressure ≥90 mmHg.

Electrocardiogram

Number (%) of patients with notably abnormal QTc values and QTc changes from baseline, and notably abnormal ventricular rate values at any time during treatment period (Safety set - Treatments continued or new in Stage 2)

	AEB071 200 mg BID N=57 n (%)	AEB071 400 mg OD N=51 n (%)	AEB071 300 mg BID N=53 n (%)	Placebo N=59 n (%)
QTc Fridericia's formula (ms)				
>= 500 ms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increase >20% from baseline	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Increase >30 ms from baseline	7 (12.3)	7 (13.7)	12 (22.6)	5 (8.5)
Increase >60 ms from baseline	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular rate (bpm)				
> 100 bpm	7 (12.3)	7 (13.7)	9 (17.0)	2 (3.4)
< 60 bpm	13 (22.8)	18 (35.3)	17 (32.1)	26 (44.1)
Fridericia's formula: QTc = QT / cube root RR (s)				

Stage 1: QTcF changes from baseline (increase >30 ms from baseline) were observed in 1 patient in the AEB071 50 mg BID group; in 3 patients in AEB071 100 mg OD group (including a patient who reported QTcF of 518 msec at 2 hour post dose (9:44 am), 15 days after the first dose of the study medication); in 3 patients in AEB071 100 mg BID group and 1 patient in the AEB071 200 mg OD group.

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