Sponsor

Novartis

Generic drug name

SAB378 [Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone]

Trial indication(s)

Postherpetic neuralgia (PHN)

Protocol number

CSAB378A2201

Protocol title

A multicenter, double-blind, randomized, placebo-controlled, parallel-group study to evaluate the safety and efficacy of SAB378 (15 mg tid) administered orally for 4 weeks to patients with postherpetic neuralgia (PHN)

Phase of Drug Development

Phase IIA

Study Start/End Dates

13 Sept 2005 to 05 Jun 2006

Study Design/Methodology

This was a multicentre, double-blind, randomized, parallel group, proof of efficacy study comparing SAB378 15 mg tid with placebo for treatment of PHN. Dose of study medication was titrated at 2 day intervals over the first 6 days of treatment, increasing the dose from 15 to 30 (dosed bid) to 45 mg/day (dosed tid), and maintaining the maximum tolerated dose for the subsequent 3 weeks of

double-blind treatment. A one week follow-up phase occurred after the treatment phase to detect any withdrawal symptoms when patients were no longer taking study drug, and a follow-up telephone call was made at 4 weeks after the last dose of study drug to collect AEs and any unusual reactions to light.

Centers

The study was conducted at 17 centres in 5 countries: Canada (2), Germany (4), United Kingdom (3), Netherlands (6), Sweden (2)

Objectives:

To demonstrate the efficacy of SAB378 in patients with PHN by testing the hypothesis that SAB378 15 mg tid is superior to placebo for reduction in pain intensity measured on the 11 point numerical rating scale (NRS) during the last week of double-blind (DB) treatment compared to baseline.

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

SAB378 15 mg hard gelatine capsules (HGC) was taken orally; dose was up-titrated from 15 mg od to 15 mg bid to 15 mg tid at 2 day intervals over the first 6 days (or 10 days if not well tolerated).

Statistical Methods

The primary efficacy variable was analyzed at an overall level of $\alpha = 10\%$ (one-sided test) in the PP population, using an analysis of covariance model (ANCOVA) with treatment, concomitant PHN medication (yes/no) and center as factors and the pain intensity rating at baseline as covariate. The least squares mean difference between SAB378 and placebo was calculated and the associated one-sided confidence interval presented, where the lower confidence limit for SAB378 minus placebo was considered to be minus infinity. Sensitivity analysis in the ITT population was also performed. Supportive analyses of the primary variable: pain intensity rating (NRS) corrected for rescue medication use and subgroup analysis by PHN co-medication use (yes/no) were also performed by ANCOVA. Pain intensity rating (NRS) 30% and 50% response rates were analyzed by logistic regression. Daily mean pain intensity ratings recorded in the patients' diaries were presented graphically versus time to evaluate onset of therapeutic effect.

Study Population:

Inclusion Criteria:

- male or female outpatients, aged 50 years and older
- with history of PHN for at least 3 months after healing of a herpes zoster skin rash

- with pain intensity due to PHN at least 5 on the 11 point NRS in the 24 hours preceding visit 1
- with average pain intensity due to PHN at least 5 on the 11 point NRS in the pre-randomization phase
- with pain intensity at least 50 mm on a 100 mm VAS in the last seven days prior to randomization
- who completed NRS ratings for at least four entire days in the patient diary in the last seven days prior to randomization
- women of non-child bearing potential
- men who are surgically sterilized or practicing reliable contraceptive methods
- who were not receiving concomitant medication for PHN, or were maintained on a stable dose of one allowed concomitant PHN medication (e.g. pregabalin, gabapentin, tricyclic antidepressants) for at least one month prior to randomization
- who had given informed consent according to the legal requirements of their respective countries

Exclusion Criteria:

- who had other pain, which could confound the assessment of the neuropathic pain due to PHN
- with skin conditions in the area affected by the neuralgia that could alter sensation
- having neurolytic or neurosurgical treatment for PHN
- who were in an immunocompromised state, e.g. have a known or suspected chronic infectious disease including HIV or hepatitis B or C
- with clinically significant psychiatric diagnoses, in particular depression, that would impair their reliable participation in the trial, or patients with significant psychosocial problems that could be related to pain complaints
- who were women of child-bearing potential
- with body mass index (BMI) > 35 kg/m 2
- with low blood pressure (systolic blood pressure <90 mmHg and/or diastolic blood pressure <60 mmHg), or orthostatic hypotension (defined as a supine-standing systolic BP drop >20 mmHg or a supine-standing diastolic BP drop >10 mmHg) at baseline
- with history of cerebrovascular disease (confirmed transient ischemic attacks, reversible ischemic neurologic deficits, and/or stroke)
- with symptomatic coronary disease or history of heart failure
- with any advanced, severe, or unstable disease that may interfere with study evaluations or put the patient at special risk
- who were receiving moderate/strong opioids (e.g. morphine, tramadol, oxycontine), carbamazepine and lidoderm patch during one month prior to randomization
- who have a history or evidence of alcohol or drug abuse within the past year
- who had used cannabis or derivatives within the past 6 months, unless these products were used successfully for pain relief, in which case, they were to be discontinued one month prior to randomization
- who were known to be hypersensitive to the ingredients of the SAB378 capsule, or to cannabinoid agonists
- who had received an experimental treatment within the past month

- who had a history of poor compliance, or were unlikely to comply with study Requirements
- who had a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, including localized basal cell carcinoma of the skin
- who foresee intensive UV exposure during the study (such as solar exposure on the beach, mountain sports, UV radiation by suntan lamps) or those with inherent sensitivity to sun

Participant Flow Table

Patient disposition - n (%) of patients (All patients)

	SAB378 n (%)	Placebo n (%)	Total n (%)
Total no. of patients:			
Screened			127
Randomized	44 (100.0)	45 (100.0)	89 (100.0)
Treated	44 (100.0)	45 (100.0)	89 (100.0)
Completed	38 (86.4)	41 (91.1)	79 (88.8)
Discontinued	6 (13.6)	4 (8.9)	10 (11.2)
Main reason for discontinuation:			
Adverse Event(s)	6 (13.6)	2 (4.4)	8 (9.0)
Abnormal test procedure result(s)	0	1 (2.2)	1 (1.1)
Subject withdrew consent	0	1 (2.2)	1 (1.1)

Baseline Characteristics

Demographic summary by treatment (Safety population)

	SAB378 N=44	Placebo N=45	Total N=89
Age - n (%)			
<65	10 (22.7)	5 (11.1)	15 (16.9)
>=65	34 (77.3)	40 (88.9)	74 (83.1)
Age (years)			
n	44	45	89
Mean (SD)	70.5 (8.24)	72.8 (7.04)	71.7 (7.70)
Median	69.0	73.0	71.7
Min - max	51 - 90	57 - 88	51 - 90
Sex - n (%)			
Male	20 (45.5)	26 (57.8)	46 (51.7)
Female	24 (54.5)	19 (42.2)	43 (48.3)
Race - n (%)			
Caucasian	44 (100.0)	45 (100.0)	89 (100.0)
Height (cm)			
n	44	45	89
Mean (SD)	167.5 (10.48)	168.3 (10.10)	167.9 (10.24)
Median	166.5	168.0	167.0
Min - max	146 - 193	143 - 187	143 - 193
Weight (kg)			
n	44	45	89
Mean (SD)	78.18 (12.585)	78.17 (12.231)	78.17 (12.337)
Median	80.00	79.50	79.50
Min - max	50.4 - 108.0	46.0 - 105.0	46.0 - 108.0
BMI (kg/m^2)			
n	44	45	89
Mean (SD)	27.78 (3.227)	27.60 (3.779)	27.69 (3.498)
Median	27.96	27.75	27.75
Min - max	22.0 - 35.2	18.4 - 38.1	18.4 - 38.1

Summary of Efficacy

Primary Outcome Result(s)

Change from baseline in pain intensity rating (NRS): treatment comparisons at primary endpoint (PP and ITT populations)

Population Treatment	N	n	LSM change	Difference SAB378 - placebo	One-sided 90% CI	One-sided p-value
PP						
SAB378	36	36	-1.0	-0.3	(-infinity, 0.1)	0.1726
Placebo	38	38	-0.6			
ITT						
SAB378	42	42	-0.7	-0.2	(-infinity, 0.2)	0.2666
Placebo	44	44	-0.6			

Primary Endpoint refers to the last 7 days of the double-blind treatment phase, days 22 – 28.
n is the number of patients with both baseline and endpoint measurements.
LSM change = least squares mean change from baseline to endpoint.
ANCOVA model with treatment, concomitant PHN medication use and center as factors and baseline value as covariate. Comparison with placebo tested at a one-sided 10% level of significance.
At visit 5, the preceding 14 days' ratings were averaged. At screening, the rating in the preceding 24 hours was used. Primary Endpoint refers to the last 7 days of the double-blind treatment phase, days 22 – 28.
† Only patients with valid measurements for the comparisons are included in the changes provided. All PP patients had valid measurements at baseline visit 2 and at visits 3, 4 and 5. Therefore mean changes from baseline at these visits and at endpoint can be obtained by subtracting the baseline mean from the visit mean.
na = not applicable

Summary of Safety

Safety Results

Adverse events overall and most frequently affected primary system organ classes (>5% in either group) during double-blind phase - n (%) of patients (Safety population)

	SAB378 N=44 n (%)	Placebo N=45 n (%)
Total number of patients with any AE(s) in the double-blind phase	36 (81.8)	30 (66.7)
Primary system organ class		
Gastrointestinal disorders	24 (54.5)	12 (26.7)
Nervous system disorders	24 (54.5)	9 (20.0)
General disorders and administration site conditions	10 (22.7)	8 (17.8)
Ear and labyrinth disorders	5 (11.4)	0
Eye disorders	4 (9.1)	1 (2.2)
Psychiatric disorders	4 (9.1)	1 (2.2)
Infections and infestations	3 (6.8)	7 (15.6)
Respiratory, thoracic and mediastinal disorders	1 (2.3)	3 (6.7)
Musculoskeletal and connective tissue disorders	0	3 (6.7)

Primary SOCs are arranged in descending order of frequency in the SAB378 group.

Most frequent AEs (>5% in either group in total safety population) during double-blind phase - n (%) of patients (Safety population, total and by PHN co-medication subgroups: yes/no)

	Total safety population		PHN co-medication = Yes		PHN co-medication = No	
	SAB378 N=44 n (%)	Placebo N=45 n (%)	SAB378 N=19 n (%)	Placebo N=30 n (%)	SAB378 N=25 n (%)	Placebo N=15 n (%)
Number of patients with any AE in DB phase	36 (81.8)	30 (66.7)	15 (78.9)	20 (66.7)	21 (84.0)	10 (66.7)
Adverse Event						
Dizziness	16 (36.4)	3 (6.7)	8 (42.1)	3 (10.0)	8 (32.0)	0
Dry mouth	15 (34.1)	4 (8.9)	7 (36.8)	3 (10.0)	8 (32.0)	1 (6.7)
Fatigue	8 (18.2)	4 (8.9)	4 (21.1)	4 (13.3)	4 (16.0)	0
Nausea	6 (13.6)	3 (6.7)	3 (15.8)	3 (10.0)	3 (12.0)	0
Somnolence	6 (13.6)	0	3 (15.8)	0	3 (12.0)	0
Constipation	5 (11.4)	0	1 (5.3)	0	4 (16.0)	0
Headache	4 (9.1)	5 (11.1)	1 (5.3)	4 (13.3)	3 (12.0)	1 (6.7)
Vertigo	4 (9.1)	0	1 (5.3)	0	3 (12.0)	0
Diarrhea	2 (4.5)	4 (8.9)	1 (5.3)	3 (10.0)	1 (4.0)	1 (6.7)

AE preferred terms are arranged in descending order of frequency in the Total/SAB378 group

Adverse events during follow-up phase - n (%) of patients (Safety population)

	SAB378 N=38 n (%)	Placebo N=41 n (%)
Number of patients with any AE(s) in the follow-up phase	8 (21.1)	2 (4.9)
AE preferred term		
Atrial flutter	1 (2.6) SAE, severe, ns	0
Tachyarrhythmia	1 (2.6) SAE, severe, ns	0
Photopsia (occasional flashes of light)	1 (2.6) mild, suspected	0
Diarrhea	1 (2.6) mild, ns	0
Nausea	1 (2.6) mild, ns	0
Vomiting	1 (2.6) mild, ns	0
Immunisation reaction (to flu vaccination)	1 (2.6) mild, ns	0
Nasopharyngitis	1 (2.6) mild, ns	0
Fall	1 (2.6) mild, ns	0
Aspartate aminotransferase increased	1 (2.6) mild, suspected	0
Headache	1 (2.6) mild, ns	1 (2.4) mild, suspected
Rhinorrhea	1 (2.6) mild, ns	0
Hypertension	0	1 (2.4) mild, ns

ns = not suspected to be related to study drug

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events during double-blind phase – n (%) of patients (Safety population)

	SAB378 N=44 n (%)	Placebo N=45 n (%)
Patients with AE(s)	36 (81.8)	30 (66.7)
Serious or other significant events:		
Death	0	0
SAE(s) (non-fatal)	0	0
Discontinued due to any AE(s)	6 (13.6)	2 (4.4)
AE(s) leading to dose adjustment or temporary interruption	8 (18.2)	2 (4.4)
Significant CNS-related AEs †	20 (45.5)	3 (6.7)

† Includes patients who had AEs with preferred terms: dizziness, vertigo, disturbance in attention or feeling drunk.

Discontinuations due to AEs - n (%) of patients (Safety population)

	SAB378 N=44 n (%)	Placebo N=45 n (%)
Number of patients discontinued due to AE(s)	6 (13.6)	2 (4.4)
Adverse Event		
Dizziness	3 (6.8)	0
Nausea	2 (4.5)	0
Vertigo	1 (2.3)	0
Dry mouth	1 (2.3)	0
Abdominal pain upper	1 (2.3)	0
Constipation	1 (2.3)	0
Feeling abnormal	1 (2.3)	0
Gait disturbance	1 (2.3)	0

Contusion	1 (2.3)	0
Drug toxicity	1 (2.3)	0
Fall	1 (2.3)	0
Burning sensation	1 (2.3)	0
Headache	1 (2.3)	0
Speech disorder	1 (2.3)	0
Disorientation	1 (2.3)	0
Diarrhea	0	1 (2.2)
Sinusitis	0	1 (2.2)

AE preferred terms are arranged in descending order of frequency in the SAB378 group. Patients can have more than one AE leading to discontinuation and hence appear in more than one category.

AEs leading to study drug dose adjustment or temporary interruption - n (%) of patients (Safety population)

	SAB378 N=44 n (%)	Placebo N=45 n (%)
Number of patients with AEs leading to study drug dose adjustment or temporary interruption	8 (18.2)	2 (4.4)
Adverse Event		
Dry mouth	3 (6.8)	0
Vertigo	2 (4.5)	0
Nausea	2 (4.5)	1 (2.2)
Dizziness	1 (2.3)	0
Sleep disorder	1 (2.3)	0
Abdominal pain upper	1 (2.3)	0
Vomiting	1 (2.3)	0
Fatigue	1 (2.3)	0
Feeling abnormal	1 (2.3)	0
Bronchitis	0	1 (2.2)

AE preferred terms are arranged in descending order of frequency in the SAB378 group. Patients can have more than one AE leading to study drug adjustment or temporary interruption and hence appear in more than one category.

Other Relevant Findings

None

Date of Clinical Trial Report

01-Nov-2006