Sponsor

Novartis

Generic Drug Name

BGG492 (selurampanel)

Therapeutic Area of Trial

Partial-onset seizures

Approved Indication

Investigational

Protocol Number

CBGG492A2212

Title

A multicenter, open-label, follow-up study to evaluate the long-term safety and tolerability of BGG492 TID as adjunctive therapy in patients with partial onset seizures completing double-blind, placebo-controlled study CBGG492A2207 or CBGG492A2211..

Study Phase

Phase II

Study Start/End Dates

Study initiation date: 02-Jun-2011 (first patient first visit)

Study completion date: 04-Jul-2012 (last patient last visit)

Study Design/Methodology

This was a multicenter, flexible dose (BGG492 50 mg to 150 mg TID), long-term (30 weeks), open-label extension study in patients with partial onset seizures. Patients who completed the 10-week Double-blind Treatment Evaluation Phase plus one week of dose-tapering (through Visit 9) in study CBGG492A2207 (CBGG492A2211 had no randomized patients) and who met the inclusion/exclusion criteria for this open-label extension study were to continue receiving BGG492 treatment if deemed acceptable by the investigator and consented to by the patient.

Centers

A total of 16 study centers in 6 countries which included - Germany (five centers), Hungary (three centers), Poland (one center), Slovakia (two centers), South Korea (two centers) and United States (three centers).

Publication

None

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

BGG492 50 mg hard gelatin capsules for oral administration at 50 mg TID, 100 mg TID or 150 mg TID.

Statistical Methods

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) was calculated for continuous variables (e.g. blood pressure), and frequency counts and percentages is given for categorical variables (e.g. AEs).

Demographic and background information were summarized using frequency distributions for categorical variables and descriptive statistics (mean, standard deviation, minimum, median and maximum) for continuous variables. The information is presented based on all treated extension set. Medical history/current medical condition before the start of open-label extension study was summarized by system organ class and preferred term of the MedDRA dictionary.

No statistical hypothesis was tested.

Adverse events were summarized by presenting the number and percentage of patients having any AE by primary system organ class and/or preferred term. AE by severity, drug related AEs, AEs leading to premature discontinuation of study drug, death and serious AEs are presented in a similar format as all AEs. Laboratory and vital sign data were summarized by presenting summary statistics of values and change from baseline by visit, by presenting frequency of patients with clinically notable changes (baseline to most extreme extension study value) and shift tables. ECG intervals were summarized by presenting summary statistics for change from baseline values by visit, frequency of clinically notable ECG abnormalities. The (uncorrected) QT interval was corrected according to the Bazett's and Fridericia formulae.

Summary tables for lab, vital sign and ECG used data at scheduled visits and no imputation was done for missing data, except that for patients who discontinued the study early on study drug.

Sample size calculation was not based on power calculations. The number of patients enrolled in this study depended on the number of patients who completed the core study, CBGG492A2207, and the percentage of these completers assumed to be eligible for the extension and to sign the ICF to participate in the extension study. Based on the protocol for CBGG492A2207, approximately 65 patients from the study were expected to complete the core study, assuming 95% of the patients participate in the extension study and sign the extension study ICF, approximately 62 patients were expected to enter the extension.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Patients eligible for inclusion in this study had to fulfill **all** of the following criteria

1. Had completed the 10 week Double-Blind Treatment Evaluation Phase plus one week of dose-tapering (Visit 9, Day 78) in study CBGG492A2207, cooperated with the study procedures and had not experienced persistent tolerability issues;
2. In the opinion of the investigator a reasonable benefit from the long-term administration of BGG492 was to be expected for all patients who wished to continue BGG492 treatment;
3. Male and female outpatients age 18 to 66 years (inclusive) with weight of ≥ 45 Kg (99 lb);
4. Were currently treated with a stable dose of one or a maximum of three licensed AEDs and were known to take their medication(s) as directed.
5. Were reliable and willing to make themselves available for the study period and were able to record seizures and report adverse events themselves or have a caregiver who could record and report the events;
6. Had provided written informed consent before any extension assessment was performed.

Exclusion criteria

1. History of status epilepticus or seizure clusters occurring during Study CBGG492A2207 or in the period between the end of study CBGG492A2207 and the start of study CBGG492A2212 for patients experiencing a treatment gap;
2. Had been treated with: felbamate; vigabatrin; monoamine oxidase (MAO) inhibitors, tricyclic-antidepressants and narcotic analgesics; L-Dopa formulations and concomitant medication that are potential inhibitors of OATP transporters.
3. No physical examination changes suggestive of progressive neurological changes (e.g. Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis) during Study CBGG492A2207;
4. History of hypersensitivity to the study drug or to drugs of similar chemical classes (e.g. sulfonamides);
5. Use of other investigational drugs apart from BGG492 either at the time of enrollment in the extension study or within 5 half-lives prior to enrollment in the extension study if the experimental medication was taken during the potential treatment gap between the studies;
6. Pregnant or nursing (lactating) women.

Participant Flow

Patient disposition through the end of open-label extension phase (Weeks 1 to 26) (All treated extension set)

Disposition Primary reason	BGG492 TID N=51 n (%)
Completed	45 (88.2)
Prematurely discontinued study medication	6 (11.8)
Adverse Event(s)	3 (5.9)
Abnormal test procedure result(s)	1 (2.0)
Unsatisfactory therapeutic effect	1 (2.0)
Subject withdrew consent	1 (2.0)

Percentages refer to the total number of patients in all treated extension set.
Reasons for discontinuation are presented in order of descending frequency.

Patient disposition through end of study (All treated extension set)

Disposition Primary reason	BGG492 TID N=51 n (%)
Completed	43 (84.3)
Prematurely discontinued study	8 (15.7)
Adverse Event(s)	3 (5.9)
Subject withdrew consent	2 (3.9)
Abnormal test procedure result(s)	1 (2.0)
Lost to follow-up	1 (2.0)
Unsatisfactory therapeutic effect	1 (2.0)

Percentages refer to the total number of patients in all treated extension set.
Reasons for discontinuation are presented in order of descending frequency.

Baseline Characteristics

Demographic summary (All treated extension set)

Demographic variable	BGG492 TID N=51
Age (years)	
n	51
Mean (SD)	39.2 (11.11)
Median	37.0

Range	(22, 63)
Age groups (years) [n (%)]	
18-40	30 (58.8)
41-65	21 (41.2)
Sex [n (%)]	
Male	22 (43.1)
Female	29 (56.9)
Race [n (%)]	
Caucasian	33 (64.7)
Asian	18 (35.3)
Ethnicity [n (%)]	
Hispanic/Latino	2 (3.9)
Other	49 (96.1)
Weight (kg)	
n	51
Mean (SD)	71.6 (15.59)
Median	71.0
Range	(49.0, 124.0)
Height (cm)	
n	51
Mean (SD)	168.3 (10.53)
Median	168.0
Range	(146.0, 192.0)
BMI (kg/m²)	
n	51
Mean (SD)	25.2 (4.61)
Median	24.4
Range	(17.7, 41.9)
Region [n (%)]	
Asia	18 (35.3)
North America	3 (5.9)
Europe	30 (58.8)

Percentages refer to the total number of patients in all treated extension set.

Region, race, height and ethnicity are obtained from the database in the double-blind study. All other information is collected pre-dose at Visit 1 extension study. If patient did not have a treatment gap then weight from the last visit in the double-blind study was used.

BMI = weight (kg)/height (m)²

Disease characteristics (All treated extension set)

Background characteristic	BGG492 TID N=51
Duration of partial epilepsy (years)	
n	51
Mean (SD)	20.3 (11.47)
Median	20.6
Range	(3.4, 52.9)
Partial epilepsy diagnosis with aura* [n (%)]	
Yes	21 (41.2)
No	30 (58.8)
Number of different AEDs taken since diagnosis of partial epilepsy*	
n	51
Mean (SD)	6.2 (3.01)
Median	6.0
Range	(2, 12)
Number of different AEDs since diagnosis by category* [n (%)]	
1-3 AEDs	12 (23.5)
4-6 AEDs	18 (35.3)
≥7 AEDs	21 (41.2)
AEDs strata at baseline* [1] [n (%)]	
Stratum 1	40 (78.4)
Stratum 2	11 (21.6)
Number of AEDs at baseline* [n (%)]	
One	1 (2.0)
Two	36 (70.6)
Three	14 (27.5)
AEDs at baseline* [n (%)]	
Carbamazepine	18 (35.3)
Lacosamide	7 (13.7)
Lamotrigine	16 (31.4)
Levetiracetam	17 (33.3)
Oxcarbazepine	11 (21.6)

Phenobarbital	1 (2.0)
Phenytoin	1 (2.0)
Pregabalin	2 (3.9)
Topiramate	9 (17.6)
Valproate	15 (29.4)
Zonisamide	12 (23.5)
Other AEDs	5 (9.8)
Number of AEDs at Day 1 of open-label study [n (%)]	
One	1 (2.0)
Two	31 (60.8)
Three	19 (37.3)
AEDs at Day 1 of open-label study [n (%)]	
Carbamazepine	18 (35.3)
Lacosamide	8 (15.7)
Lamotrigine	15 (29.4)
Levetiracetam	17 (33.3)
Oxcarbazepine	11 (21.6)
Phenobarbital	1 (2.0)
Phenytoin	3 (5.9)
Pregabalin	2 (3.9)
Topiramate	9 (17.6)
Valproate	15 (29.4)
Zonisamide	12 (23.5)
Other AEDs	9 (17.6)
Presurgical evaluation for epilepsy performed?* [n (%)]	
Yes	24 (47.1)
Not eligible	7 (13.7)
Eligible, surgery performed	6 (11.8)
Eligible, surgery not performed	11 (21.6)
No	27 (52.9)
Did MRI findings rule out progressive neurological changes?* [n (%)]	
n [2]	51 (100.0)
Yes	10 (19.6)
No	41 (80.4)
Baseline total partial seizure frequency per 28 days*	
n	51

Mean (SD)	18.8 (23.08)
Median	9.6
Range	(3.7, 136.0)
Seizure types at 4-week baseline period* [n (%)] [3]	
Simple partial seizures without motor signs	11 (21.6)
Simple partial seizures with motor signs	14 (27.5)
Complex partial seizures	38 (74.5)
Partial seizures evolving to secondary generalized seizures	10 (19.6)
Non-partial seizures	0
Hospital Anxiety and Depression Scale (HADS) at baseline*	
Total score (HADS)	
n	51
Mean (SD)	13.1 (7.44)
Median	11.0
Range	(1, 34)
Anxiety subscale (HADS-A) [4]	
n	51
Mean (SD)	7.0 (4.14)
Median	7.0
Range	(0, 19)
Depression subscale (HADS-D) [4]	
n	51
Mean (SD)	6.1 (4.41)
Median	5.0
Range	(1, 18)

AED = Antiepileptic drug.

* Information obtained from the baseline period in the double-blind study.

[1] Stratum 1 is comprised of patients using one or more of the following AEDs at baseline: carbamazepine, oxcarbazepine, phenytoin or lamotrigine; Stratum 2 is comprised of patients not using any Stratum 1 AED drug at baseline.

[2] n is the number of patients who had MRI performed and serves as denominator for this category.

[3] Patients with multiple seizure types can be counted more than once.

[4] Scores of 0-7 are considered normal, with 8-10 mild, 11-14 moderate and 15-21 severe.

Primary outcome Result(s)

Please refer to Safety Results section.

Secondary Outcome Result(s)

Change from the original baseline period in double-blind study to open-label extension maintenance phase (Weeks 5 to 26), by duration of exposure (All treated extension set)

		BGG492 TID N=51			
Duration of exposure	**Statistics**	**Baseline**	**Post-baseline**	**Change**	**% Change [1]**
Double-blind baseline (Weeks -4 to -1)	n	51			
	Mean (SD)	18.8 (23.08)			
	Median	9.6			
	Range	(3.7, 136.0)			
Open-label maintenance phase (Weeks 5 to 26)	n	50	50	50	50
	Mean (SD)	18.8 (23.32)	9.3 (8.41)	9.5 (20.40)	34.2 (47.86)
	Median	9.6	6.4	3.7	43.4
	Range	(3.7, 136.0)	(0.0, 30.1)	(-6.9, 123.9)	(-126.4, 100.0)
Weeks 5 to 13	n	50	50	50	50
	Mean (SD)	18.8 (23.32)	9.1 (8.93)	9.7 (21.14)	34.6 (54.64)
	Median	9.6	6.4	3.8	47.4
	Range	(3.7, 136.0)	(0.0, 34.8)	(-10.6, 129.4)	(-135.1, 100.0)
Weeks 14 to 26	n	48	48	48	48
	Mean (SD)	18.7 (23.64)	9.6 (9.15)	9.0 (20.48)	34.2 (45.79)
	Median	9.6	6.7	3.2	46.2
	Range	(3.7, 136.0)	(0.0, 35.3)	(-12.1, 120.2)	(-117.7, 100.0)

Change in seizure frequency from baseline = B-T, B=Seizure frequency per 28 days during original baseline period in double-blind study, T=Seizure frequency per 28 days during the specified period.

A negative change indicates an increase from baseline and a positive change indicates a reduction from baseline.

Percent change in seizure frequency from baseline = 100 (B-T)/B, B=Seizure frequency per 28 days during original baseline period in double-blind study, T=Seizure frequency per 28 days during the

specified period.

Seizure frequency per 28 days is calculated as: (seizure frequency during the specified period / the number of days the seizure information were provided) × 28.

Only patients with both baseline and corresponding post-baseline values are included.

[1] Only patients with non-zero seizure frequency count at baseline are included in percent change calculation.

Number and percent of responders during the open-label extension maintenance phase (Weeks 5 to 26), by duration of exposure (All treated extension set)

Duration of exposure	Total n [1]	Responder [2] n (%)
Open-label maintenance phase (Weeks 5 to 26)	50	22 (44.0)
Maintenance (Weeks 5 to 13)	50	23 (46.0)
Maintenance (Weeks 14 to 26)	48	22 (45.8)

[1] n is the number of patients with non-missing seizure information during the specified period.

[2] Responder is defined as patients with a 50% or greater reduction in total partial seizure frequency per 28 days from original baseline period.

Safety Results

Incidence of adverse events during the open-label extension study (Weeks 1 to 30) (>5% frequency), regardless of study drug relationship, by primary system organ class (All treated extension set)

Primary system organ class	BGG492 TID N=51 n (%)
-Any primary system organ class	
-Total	39 (76.5)
Ear and labyrinth disorders	4 (7.8)
Eye disorders	3 (5.9)
General disorders and administration site conditions	8 (15.7)
Infections and infestations	5 (9.8)
Injury, poisoning and procedural complications	5 (9.8)
Musculoskeletal and connective tissue disorders	4 (7.8)
Nervous system disorders	24 (47.1)
Psychiatric disorders	3 (5.9)
Skin and subcutaneous tissue disorders	3 (5.9)

Primary system organ classes are presented alphabetically;

A patient with multiple AEs within a SOC is counted only once in the SOC.

Number (%) of patients reporting common AEs during the open-label extension study (Weeks 1 to 30) (>5% frequency), by preferred term (All treated extension set)

Preferred term	BGG492 TID N=51 n (%)
-Any primary system organ class	
-Total	39 (76.5)
Dizziness	14 (27.5)
Somnolence	9 (17.6)
Fatigue	5 (9.8)
Contusion	4 (7.8)
Vertigo	4 (7.8)
Nasopharyngitis	3 (5.9)

Preferred terms are sorted by descending order of incidence.

Deaths, other serious adverse events and adverse events leading to discontinuation during the open-label extension study (Weeks 1 to 30) (All treated extension set)

	BGG492 TID N=51 n (%)
Patients with AE(s)	39 (76.5)
Serious or other significant events	
Death	0
SAE(s) (non fatal)	1 (2.0)
Discontinued due to AE(s)	3 (5.9)
Discontinued due to SAE(s)	1 (2.0)

Patients may be counted in more than one category.

Other Relevant Findings

None

Date of Clinical trial Report

29-May-2013

Date Inclusion Novartis Clinical trial Results Database

28 June 2013