Sponsor

Novartis

Generic Drug Name

BGG492

Therapeutic Area of Trial

Therapy refractory partial seizures

Approved Indication

Investigational

Study Number

CBGG492A2202

Title

A multicenter, double-blind, randomized, placebo-controlled, two-arm parallel-group study of BGG492 as monotherapy in individuals with refractory partial seizures undergoing inpatient evaluation for epilepsy surgery

Phase of Development

Phase II

Study Start/End Dates

31-Mar-2009 (first patient first visit) to 05-Aug-2010 (last patient last visit)

Study Design/Methodology

This was a multicenter, double-blind, randomized, placebo-controlled, 2-arm parallel-group study. Approximately 45 patients with refractory partial seizures who were undergoing an evaluation for surgery and receiving no more than 2 AEDs at time of dosing with BGG492 were to be randomized (1:1) to receive either BGG492 (25 mg and 50 mg t.i.d.) or Placebo to ensure that 40 patients complete the evaluation period.

Centres

4 centers in Germany

Publication

None

Objectives

Primary objective(s)

- To determine the efficacy of BGG492 vs. Placebo in reducing the seizure rate when administered orally for up to 7 days as monotherapy in patients with refractory partial seizures who were undergoing an inpatient pre-surgical diagnostic evaluation for epilepsy surgery.

Secondary objective(s)

- To determine the efficacy of BGG492 vs. Placebo in reducing the seizure rate when administered orally for up to 9 days (during Titration and Monotherapy phases) in patients with refractory partial seizures who were undergoing an inpatient pre-surgical diagnostic evaluation for epilepsy surgery.
- To determine the efficacy of BGG492 vs. Placebo in reducing the seizure rate when administered orally for up to 2 days (during Titration phase) in patients with refractory partial seizures who were undergoing an inpatient pre-surgical diagnostic evaluation for epilepsy surgery.
- To evaluate the safety and tolerability of BGG492 repeated dose over 9 days in patients with refractory partial seizures
- To determine the plasma levels of BGG492 in patients with refractory partial seizures.
- To determine if BGG492 changes the seizure type patterns and/or seizure duration as measured by the seizure types observed and the total seizure duration per day

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

Hard gelatin capsules containing BGG492 in 5 mg strength administered orally in a batch of 5 capsules (25 mg) thrice daily on Day 1.

Hard gelatin capsules containing BGG492 in 50 mg strength administered orally as 1 capsule thrice daily from Day 2-9.

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

Hard gelatin capsules containing placebo, administered orally in a batch of 5 capsules thrice daily on Day 1 and 1 capsule thrice daily from Day 2-9.

Criteria for Evaluation

Primary variable

- The primary variable is the seizure rate during the Monotherapy phase.

Secondary variables

- The seizure rates during the Titration and Combined phases;
- Seizure rate by type of seizure during the entire study period; and
- Seizure duration measured as percentage of the observation period.

Safety and tolerability

Safety variables consisted of collecting all adverse events (AEs), serious adverse events (SAE), with their severity and relationship to study drug. They included the regular monitoring of laboratory values (hematology, blood chemistry and urinalysis) and regular assessments of vital signs, ECG, physical condition, and body weight. Additional safety assessments as specified by the protocol included special laboratory test results (Thyroid Stimulating Hormone, thyroid hormones etc.) and evaluations of neurological and neuropsychological results at the protocol specified times.

Pharmacokinetics

Blood samples (3 mL) for pharmacokinetic evaluation were collected from a forearm vein (direct venipuncture or from an indwelling cannula) into an EDTA tube at each time point. All samples were processed as described in the protocol (Appendix 16.1.1) and stored frozen at 20°C until analysis. Analysis of BGG492 in plasma was performed using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method with a LLOQ set at 0.5 ng/mL or lower.

Other

Exploratory Biomarker assessments (optional): Exploratory Biomarker assessments GluR3 autoantibody determination. Blood collection: one 2 mL blood sample to obtain 1 mL of serum at Day -1 (baseline)

Pharmacogenetic assessments (optional): Pharmacogenetic blood collection was done at baseline. A single 6mL blood sample will be collected in EDTA tubes at baseline from each patient who agrees, in writing, to participate in pharmacogenetic evaluations.

Statistical Methods

For the primary analysis of the primary endpoint a linear model on the log scale with treatment as a fixed effect and patient as a random effect was fitted for the seizure rate, assuming that seizures within a patient were Poisson-distributed. In other words, a Poisson distribution with a normally distributed rate on the log-scale allowing for different extent of over dispersion in the 2 groups was used as model for seizure rate.

The ratio of the seizure rates in BGG492 group and placebo group was derived from the model fit. It was assessed whether the seizure rate in the BGG492 group was statistically significantly smaller than in the placebo group (1-sided test at 5% alpha level) and whether the estimated reduction was at least a 33% reduction of seizure rate under BGG492 as compared to Placebo.

Both frequentist and Bayesian methods were used to fit this model.

The Bayesian analysis was performed to assess the posterior probabilities of following two criteria:

seizure rate under BGG492 being lower than under placebo

seizure rate under BGG492 being at least 33% lower than under placebo

For each of the parameters in the model, a non-informative prior was used.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Patients who met the following criteria were included:

- Male or female patients aged 18 to 65 years (inclusive) providing written informed consent prior to initiation of any study procedure and willing to comply with the study procedures.
- Diagnosis of partial seizures (with or without secondary generalization) and undergoing an evaluation for epilepsy surgery, based on the classification of the International League Against Epilepsy, as modified in 1981.
- Stable dosing regimen with no more than 2 (except of association of lamotrigine with valproate) AEDs prior to randomization. (Note: allowed AEDs at baseline were: valproate, lacosamide, lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, phenytoin, clobazam, topiramate, pregabalin, gabapentin)
- Willing to be hospitalized for a pre-surgical evaluation and study procedures for up to 10 days.
- Absence of evolving space-occupying lesions or progressive neurological diseases.
- Capable of communicating well with the Investigator, understanding and complying with the requirements of the study, satisfying the requirements of the protocol and having understood and signed the written informed consent prior to initiation of any study procedure after the nature of the study has been fully explained.

- Vital signs (at least the last reading out of 3 consecutive assessments) at Screening, and Baseline, within the following ranges:
    - oral body temperature between 35.0-37.5 °C
    - systolic blood pressure, 90-150 mmHg
    - diastolic blood pressure, 50-90 mmHg
    - pulse rate, 40 - 90 bpm

  And no more than a 20 mm Hg drop in systolic or 10 mmHg drop in diastolic blood pressure and increase in heart rate (>20 bpm) associated with clinical manifestation of postural hypotension, when blood pressure and pulse were taken again after 3 minutes standing.
- Women of childbearing potential using or willing to use oral, injected or implanted hormonal methods of contraception or use 2 acceptable methods of contraception, (e.g. intra-uterine device plus condom, spermicidal gel plus condom, diaphragm plus condom, etc.), from the time of Screening and for the entire duration of the study.
- Postmenopausal females with no regular menstrual bleeding for at least 1 year prior to screening or for those who reported surgical sterilization must have had the procedure at least 6 months prior to the initial dosing.
- Female patients with negative pregnancy test results at screening and baseline.
- Male patients willing to use a double-method local contraception, (e.g. spermicidal gel plus condom) for the entire duration of the study.
- Weighed at least 50 kg and had a body mass index (BMI) within the range of 18 to 35.

Exclusion criteria

Patients who met the following criteria were excluded:

- Pregnant or nursing females.
- Diagnosis of generalized seizures (with the exception of secondarily generalized seizures), based on the classification of the International League Against Epilepsy, as modified in 1981**.**
- History of frequent and/or severe status epilepticus (i.e. requiring intensive care unit treatment).
- Current treatment with phenobarbital, primidone or zonisamide (these drugs would have to be completely washed out before baseline).
- Discontinuation of chronic benzodiazepine and barbiturate therapy within 30 days prior to the baseline.
- History of electrodes implanted in the brain.
- Pseudo-seizures that may impact the interpretation of seizures observed during the study.
- Evidence on physical examination, or a history of any medically significant thyroid, cardiac, respiratory, hepatic, gastrointestinal, renal, hematologic, oncologic, psychiatric or progressive neurological disorder, requiring current medical intervention/therapy likely to have a significant impact on the outcome of this study.
- Malignancy, or a history of malignancy, within the past 5 years.
- History of clinically significant drug allergy or a known hypersensitivity to drugs of the same class to the study drug.

- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs, e.g. Gastrointestinal surgery and/or pancreatic or liver disease.
- One or more clinically relevant abnormal biochemical or hematological variables or having liver function test results exceeding 3 times the upper limit of normal (ULN) values.
- Evidence or history of drug or alcohol abuse in the 3 months preceding Screening, or evidence of such abuse as indicated by the laboratory assays conducted during Screening or Baseline.
- Mental impairment limiting the ability to comply with study requirements.
- Treatment with lamotrigine in combination with valproate
- Used (or having used within 4 weeks before initial dosing) concomitant medications that are potent inducers of CYP3A4 (e.g., ketoconazole, ritonavir, etc.) and Pgp (P-glycoprotein) (e.g. verapamil, rifampin, St John's wort), except carbamazepine, oxcarbamazepine and phenytoin.
- Participation in any clinical investigation within 4 weeks prior to initial dosing or longer if required by local regulations, and for any other limitation of participation based on local regulations.
- Donated or lost 400 mL or more of blood and/or blood components within 8 weeks prior to initial dosing, or longer if required by local regulation.
- Significant illness other than epilepsy within 2 weeks prior to initial dosing.
- History of clinically significant ECG abnormalities or a family history (grandparents, parents and siblings) of a prolonged QT-interval syndrome (as far as is known).
- Recent (within the last 3 years) and/or recurrent history of autonomic dysfunction (e.g. recurrent episodes of fainting, palpitations, etc).
- History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
- Positive Hepatitis B surface antigen (HBsAg) test result.
- History of clinically significant episodes of blurry vision and or other visual disturbances that may impact the interpretation of visual disturbances during the trial.

Number of Subjects

Patient disposition – n (%) of patients (Intent-to-treat population)

	BGG492 N=17 n (%)	Placebo N=18 n (%)	Total N=35 n (%)
Patients			
Completed	16 (94.1)	17 (94.4)	33 (94.3)
Discontinued	1 (5.9)	1 (5.6)	2 (5.7)
Main cause of discontinuation			
Subject withdrew consent	1 (5.9)	1 (5.6)	2 (5.7)

Demographic and Background Characteristics

Demographic summary by treatment group

		BGG492 N=17	Placebo N=18	Total N=35
Age (years)	Mean (SD)	40.9 (11.34)	39.6 (9.41)	40.2 (10.26)
	Median	39.0	40.5	40.0
	Range	21-56	20-61	20-61
Height (cm)	Mean (SD)	176.6 (10.12)	172.0 (11.11)	174.3 (10.75)
	Median	176.0	173.5	176.0
	Range	159-191	157-196	157-196
Weight (kg)	Mean (SD)	79.81 (18.532)	77.69 (14.701)	78.72 (16.457)
	Median	77.00	74.70	77.00
	Range	57.0-115.0	55.0-100.0	55.0-115.0
BMI (kg/m^2)	Mean (SD)	25.478 (5.2120)	26.219 (3.9899)	25.859 (4.5699)
	Median	24.327	26.747	25.594
	Range	18.81-39.79	19.44-31.74	18.81-39.79
Sex - n(%)	Male	10 (58.8 %)	10 (55.6 %)	20 (57.1 %)
	Female	7 (41.2 %)	8 (44.4 %)	15 (42.9 %)
Race - n(%)	Caucasian	17 (100.0 %)	18 (100.0 %)	35 (100.0 %)
Ethnicity - n(%)	Hispanic/Latino	0 (0.0 %)	1 (5.6 %)	1 (2.9 %)
	Other	17 (100.0 %)	17 (94.4 %)	34 (97.1 %)

Epilepsy disease history by treatment group

	BGG492 N=17	Placebo N=18
No. of seizures by seizure type during the 4 weeks prior to screening; Median (Range)		
Simple partial seizures	0.0 (0-1)	0.0 (0-12)
Complex partial seizures	5.0 (0-210)	4.0 (0-13)
Partial seizures evolving to secondarily generalized seizures	0.0 (0-1)	0.0 (0-1)
Duration of epilepsy (years)		
Mean (SD)	20.6 (14.16)	15.5 (13.41)
Median	20.7	12.4
Range	1-45	2-55

Primary Objective Result(s)

Seizure rate during the Monotherapy phase

Summary of the statistical analysis of overall seizure rate

	Seizure Rate (90% CI)				Ratio (90% CI)
Study Phase	**N**	**BGG492**	**N**	**Placebo**	**BGG492:Placebo**
Titration	17	0.38 (0.13, 1.09)	18	1.27 (0.71, 2.28)	0.30 (0.09, 0.99)
Monotherapy	16	0.55 (0.31, 0.97)	17	0.64 (0.30, 1.37)	0.86 (0.33, 2.24)
Combined	17	0.59 (0.35, 1.02)	18	1.22 (0.73, 2.04)	0.49 (0.23, 1.03)

Secondary Objective Result(s)

Seizure rate during the Titration phase and Combined phases

Refer to the above table 'Summary of the statistical analysis of overall seizure rate'

Seizure rate by type of seizure

Summary of the statistical analysis of seizure type during the entire study period

	Seizure Rate (90% CI)				Ratio (90% CI)
Type of seizure	**N**	**BGG492**	**N**	**Placebo**	**BGG492:Placebo**
Simple partial seizures	17	0.02 (0.00, 0.16)	18	0.05 (0.01, 0.21)	0.33 (0.02, 5.26)
Complex partial seizures	17	0.20 (0.06, 0.61)	18	0.81 (0.43, 1.55)	0.24 (0.07, 0.89)
Secondary generalized tonic-clonic seizure	17	0.05 (0.01, 0.22)	18	0.05 (0.02, 0.16)	0.94 (0.14, 6.22)

Overall seizure duration measured as percentage of the observation period

Summary of the statistical analysis of the ratio of overall seizure duration / observed time

	Median seizure duration (min-max)				BGG492 -Placebo
Study Phase	**N**	**BGG492**	**N**	**Placebo**	**Median Difference (95% CI)**
Titration	10	0.21(0.00, 0.88)	12	0.33(0.08, 1.51)	-0.17 (-0.63, 0.04)
Monotherapy	12	0.12 (0.00, 5.21)	11	0.39(0.03, 0.76)	0.23 (-0.02, 0.39)
Combined	15	0.12(0.00, 1.04)	15	0.36(0.02, 1.27)	-0.21 (-0.32, -0.03)

Plasma levels of BGG492 in patients

Summary of main BGG492 plasma pharmacokinetic parameters following morning dose administration of 25 mg (Day 1) and 50 mg (Days 3, 6 and 9)

Parameter (Unit)	Geometric mean (%CV geo mean) Day1 N=17	Day 3 N=12	Day 6 N=6	Day 9 N=11
AUClast (ng.h/mL)	3517 (32)	7093 (33)	6142 (33)	6921 (28)
Cmax (ng/mL)	1057 (24)	2051 (25)	1854 (32)	1944 (27)
Cmin,ss (ng/mL)	na	155 (114)	150.5 (71)	161.7 (47)
Cav,ss (ng/mL)	na	1182 (33)	1024 (33)	1153 (28)
Tmax /Tmax,ss (hr)*	1.75 (1.25-2.83)	1.68 (1.25-3.22)	1.75 (1.25-2.75)	1.72 (1.17-2.75)

*median (min, max)

Safety Results

Adverse Events by System Organ Class

Study Phase: Titration

Adverse events overall and frequently affected system organ classes - n (%) of subjects (all patients)

	BGG492 N=17 n (%)	Placebo N=18 n (%)
Patients with AE(s)	6 (35.3)	7 (38.9)
System organ class		
Nervous system disorders	4 (23.5)	1 (5.6)
Gastrointestinal disorders	2 (11.8)	2 (11.1)
Psychiatric disorders	2 (11.8)	2 (11.1)
Cardiac disorders	1 (5.9)	1 (5.6)
General disorders and administration site conditions	1 (5.9)	1 (5.6)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (5.6)
Vascular disorders	0 (0.0)	1 (5.6)

arranged in descending order of frequency

Study Phase: Monotherapy

Adverse events overall and frequently affected system organ classes - n (%) of subjects (all patients)

	BGG492 N=16 n (%)	Placebo N=17 n (%)
Patients with AE(s)	9 (56.3)	9 (52.9)
System organ class		
Nervous system disorders	2 (12.5)	4 (23.5)
Cardiac disorders	2 (12.5)	2 (11.8)
Injury, poisoning and procedural complications	3 (18.8)	1 (5.9)
General disorders and administration site conditions	1 (6.3)	2 (11.8)
Musculoskeletal and connective tissue disorders	3 (18.8)	0 (0.0)
Eye disorders	1 (6.3)	1 (5.9)
Psychiatric disorders	2 (12.5)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (5.9)
Skin and subcutaneous tissue disorders	1 (6.3)	0 (0.0)
Vascular disorders	1 (6.3)	0 (0.0)

arranged in descending order of frequency

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

Study Phase: Titration

Adverse events overall and most frequent events - n (%) of subjects (all patients)

	BGG492 N=17 n (%)	Placebo N=18 n (%)
Patients with AE(s)	6 (35.3)	7 (38.9)
Preferred term		
Abdominal pain	0 (0.0)	2 (11.1)
Headache	2 (11.8)	0 (0.0)
Muscle contractions involuntary	1 (5.9)	1 (5.6)
Back pain	0 (0.0)	1 (5.6)
Diarrhoea	0 (0.0)	1 (5.6)
Dizziness	1 (5.9)	0 (0.0)
Drug withdrawal syndrome	0 (0.0)	1 (5.6)
Dry mouth	1 (5.9)	0 (0.0)
Gait disturbance	1 (5.9)	0 (0.0)
Hot flush	0 (0.0)	1 (5.6)

arranged in descending order of frequency

Study Phase: Monotherapy

Adverse events overall and most frequent events - n (%) of subjects (all patients)

	BGG492 N=16 n (%)	Placebo N=17 n (%)
Patients with AE(s)	9 (56.3)	9 (52.9)
Preferred term		
Headache	2 (12.5)	1 (5.9)
Back pain	2 (12.5)	0 (0.0)
Insomnia	2 (12.5)	0 (0.0)
Procedural site reaction	2 (12.5)	0 (0.0)
Ventricular extrasystoles	1 (6.3)	1 (5.9)
Conduction disorder	1 (6.3)	0 (0.0)
Decreased appetite	0 (0.0)	1 (5.9)
Dermatitis	1 (6.3)	0 (0.0)
Drug withdrawal syndrome	0 (0.0)	1 (5.9)
Fatigue	1 (6.3)	0 (0.0)

arranged in descending order of frequency

Serious Adverse Events and Deaths

There were no deaths, SAEs or other significant AEs reported during the study.

Other Relevant Findings

None.

Date of Clinical Trial Report

13 Jul 2011 (content final)

Date Inclusion on Novartis Clinical Trial Results Database

08 Aug 2011

Date of Latest Update

03 Aug 2011