Sponsor

Novartis

Generic Drug Name

BGG492

Therapeutic Area of Trial

Epilepsy

Approved Indication

Investigational

Study Number

CBGG492A2211

Title

A 12-week, randomized, double-blind, placebo-controlled exploratory dose-titration study to assess the antiepileptic activity of BGG492 given orally three times daily (TID) as adjunctive treatment in patients with refractory partial onset seizures

Phase of Development

II

Study Start/End Dates

17-Aug-2010 (first patient screened) to 05-Nov-2010 (last patient screened)

The study was terminated on 08-Nov-2010 prior to any patients being randomized.

Study Design/Methodology

Multicenter, randomized, double-blind, placebo controlled study evaluating 20 mg, 50 mg, 100 mg BGG492 administered three times daily compared to placebo TID dosing.

Centres

45 centers were planned in eleven countries; however, only 7 centers in six countries (Austria 1, Bulgaria 1, Estonia, 1, Latvia 1, Lithuania 1, Romania 2) screened at least one patient.

Publication

None

Objectives

Primary objective(s)

- Evaluate the efficacy of BGG492 100 mg administered orally TID compared to placebo assessed as change in seizure frequency from the 4-week baseline period to the 100 mg double-blind maintenance period (week 7-10).

Secondary objective(s)

- Evaluate the responder rate (defined as patients with a 50% or greater reduction in seizure frequency from baseline) of BGG492 administered orally TID compared to placebo during the 4-week (Weeks 7-10) double-blind maintenance period.
- Evaluate other efficacy and safety parameters during the double-blind period.

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

Oral capsules of BGG492 20 mg, 50 mg, or 100 mg three times daily

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

Oral capsules of placebo three times daily

Criteria for Evaluation

Primary variables and Secondary variables

- Seizure frequency and seizure types were to be evaluated in a comprehensive diary commencing 4-weeks prior to randomization.

Safety and tolerability

- Safety assessments were to include: adverse events (AEs), serious adverse events (SAEs), Concomitant Medications, AED medications, Laboratory assessments, Vital signs, electrocardiogram (ECG), and physical, neurological, ophthalmologic examination. The Hospital Anxiety and Depression (HADS) patient completed questionnaire was also to be completed during the treatment phase of the study to provide supplemental information. The Columbia Suicide Severity Rating Scale (C-SSRS) – was to be conducted only at US sites using a patient completed IVR questionnaire (system is validated only in English).

Pharmacology

- Blood sampling to determine plasma concentrations of BGG492, cerebrospinal fluid (CSF) BGG492 concentration (optional), and serum concentrations of AEDs were planned.

Other

- Health Economics assessments were to include the QOLIE-31 patient-completed questionnaire and resource utilization.
- iGluR3 antibody presence in blood (obligatory) was assessed as a positive result was one of the major inclusion criteria for the trial.
- Optional pharmacogenetic testing was scheduled on the day of randomization.

Statistical Methods

The primary objective of this study was to evaluate the efficacy of BGG492 100 mg (administered orally TID) compared to placebo assessed as change in seizure frequency from the 4-week baseline period (Weeks -4 to -1) to the 100 mg maintenance double-blind period (Weeks 7 – 10). The hypothesis to be tested was that there is no treatment difference in the seizure frequency per 28 days between BGG492 100 mg and the placebo during the 4-week (Weeks 7 – 10) double-blind maintenance period vs. there is a treatment difference. The treatment difference was to be tested by fitting an analysis of covariance (ANCOVA) model with the log-transformed seizure frequency per 28 days during Weeks 7 – 10 as a response variable, treatment, region and AED group as factors, baseline log seizure frequency as a covariate. Estimated ratio between treatment in seizure frequency per 28 days during Weeks 7 – 10 will be presented together with its 95% confidence interval. As supportive analysis, Wilcoxon rank-sum test was to be used to test the

treatment difference in the percent change from baseline to the Weeks 7 – 10 double-blind maintenance period in seizure frequency per 28 days. The responder rate, a secondary efficacy variable defined as patients with a 50% or greater reduction in seizure frequency from baseline between BGG and placebo was to be tested using logistic regression. Odds ratio between treatment groups will be presented together with its 95% confidence interval. Other secondary objectives were to be evaluated using either statistical models or contingency tables or summary statistics. Adverse events during the 10-week double-blind treatment evaluation period were to be summarized by presenting the number and percentage of patients having any AE by treatment group, primary system organ class and/or preferred terms. Death, serious AE, AE leading to premature discontinuation of study drug were also to be presented. Laboratory data and vital sign data were to be summarized by presenting summary statistics in change from baseline values, or presenting clinically notable values and shift tables.

Since the study was terminated before any patients were randomized, the planned analysis was significantly reduced. Demography data and the reason for why the patients screened failed were summarized and GluR3 antibody results were displayed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Male and female outpatients age 18 to 65 years (inclusive)
- Weight of = 50 kg (110 lb)
- Have a diagnosis of epilepsy (more than 2 years prior to screening) with partial seizures with or without secondarily generalized seizures according to the International League Against Epilepsy's Classification of Epileptic Seizures
- Have at least 4 partial seizures (defined as simple partial seizures with motor signs, complex partial seizures, and complex partial seizures with secondary generalization or a combination of these types for this inclusion criterion) during the 4-week baseline period and the 4 weeks immediately preceding the baseline period (retrospective and/or prospective data).
- Have no 28-day seizure-free period during the 8 weeks preceding randomization.
- Must have a positive test result for iGluR3 antibodies in the blood at screening
- Must be receiving stable treatment with 1 or a maximum of 2 AEDs

Exclusion criteria:

- Presence of only non-motor simple partial seizures
- History of psychogenic seizures
- Absences, myoclonic seizures e.g. in the context of primary generalized epilepsy
- Previous history of Lennox-Gastaut syndrome
- History of Status epilepticus or seizure clusters (where individual seizures cannot be counted according to the judgment of the investigator) occurring within 52 weeks prior to randomization.

Number of Subjects

	Total n (%)
Total number of screened patients	58 (100.0)
Screen failures	58 (100.0)
Primary reason(s) for not continuing	
Other	33 (56.9)
Unacceptable laboratory value(s)	24 (41.4)
Subject withdrew consent	1 (1.7)

Percentages refer to the total number of screened patients.
Reasons for screen failures are presented in descending order.

Demographic and Background Characteristics

Demographic Variable	Total N=58
Age (year)	
N	58
Mean	37.5
SD	10.78
Median	37.5
Minimum	18
Maximum	60
Age groups (years) - n (%)	
<18	0
18-40	34 (58.6)
41-65	24 (41.4)
>65	0
Sex - n (%)	
Male	31 (53.4)
Female	27 (46.6)
Race - n (%)	
Caucasian	57 (98.3)
Black	0
Asian	0
Native American	0
Pacific Islander	0
Other	1 (1.7)
Ethnicity - n (%)	
Hispanic/latino	1 (1.7)
Chinese	0
Indian (Indian subcontinent)	0
Japanese	0
Mixed ethnicity	0
Other	57 (98.3)
Region - n (%)	
Asia	0
North America	0
Europe	58 (100.0)

Percentages refer to the total number of screened patients.

Primary Objective Result(s)

None

Secondary Objective Result(s)

None

Safety Results

None

Adverse Events by System Organ Class

None

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

None

Serious Adverse Events and Deaths

None

Other Relevant Findings

None

Date of Clinical Trial Report

02-Nov-2011

Date Inclusion on Novartis Clinical Trial Results Database

04-Nov-2011

Date of Latest Update

02-Nov-2011