Sponsor

Novartis

Generic Drug Name

BGG492

Therapeutic Area of Trial

Migraines

Approved Indication

Investigational

Study Number

BGG492A2204

Title

A multi-centre, randomized, double-blind, parallel group, active and placebo controlled, Proof of Concept study in patients with acute migraine to assess the efficacy, safety and tolerability of single oral doses of BGG492.

Phase of Development

Phase II

Study Start/End Dates

Study initiation date: 13-May-2009 (FPV)

Study completion date: 24-Aug-2010 (LPV)

Study Design/Methodology

This was a multi-centre, randomized, double-blind, parallel group, active and placebocontrolled,
and single oral dose study in patients affected by acute migraine with or without aura for at least one year prior to study start. Patients who fulfilled the eligibility criteria were randomized (1:1:1)
to receive either a single oral dose of BGG492 (250 mg), sumatriptan (100 mg) or placebo. All the
treatments had the same appearance (gelatin capsules) and each patient received an equal number of
capsules (7) on the day of treatment. Each patient participated in a screening period of up to 28 days,
a single day treatment period (Day 1) based on when a migraine occurred, and a study completion
visit two days after the treatment day. The response to treatment was evaluated using the Migraine
Patient Diary at defined intervals both before and after dosing (up to 24 hours). If after 4

hours postdosing
no headache improvement was detected, patients were to be treated with the appropriate rescue medication. Rescue medication allowed were paracetamol, acetylsalicylic acid or ibuprofen
depending on patient medical history and Investigator's evaluation. Patients were not treated more
than once with the study medication within the trial. However, the investigator was allowed to give
rescue medication before 4 hours post dosing, if he/she deemed it necessary for the well-being of the
patient.
After completion of all the scheduled assessments patients had a study completion visit, which was to take place 2 days (± 1) after drug administration at the study site.

Centres
14 centers in 3 countries: Germany (10 centers), Spain (2 centers), United States (2 centers)

Publication

No publication

Objectives
Primary objectives
• To assess the efficacy of a single dose of BGG492 vs. placebo in patients with acute migraine
using the Migraine Patient Diary.
• To evaluate the safety and tolerability of single oral doses of 250 mg BGG492 in migraine patients.
Secondary objective
• To evaluate the improvement in pain score, sustained response rate, pain-free rate, and sustained
- pain-free rate using the Migraine Patient Diary.

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

The investigational drug, BGG492 50 mg capsule was prepared by Novartis and supplied to the Investigator.
The batch and formulation numbers of the test drug is provided below
Study drug and strength Formulation control number Batch number
BGG492 50 mg 6002147.001 AEUS/2007-0296

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

The active comparator drug, sumatriptan 50 mg and matching placebo capsules (test drug and active comparator) were prepared by Novartis and supplied to the Investigator.
The batch and formulation numbers of the active comparator and placebo are provided below

Study drug and strength	Formulation control number	Batch number
Sumptriptan 50 mg	6002638.001	E24039.1
	6002683.001	E26180.1
Placebo	3755667.030	12881.06
	6001944.010	AEUS/2008-0254
	3755667.017	H214JB

Criteria for Evaluation

Efficacy: An eligible attack for the study had to be a moderate or severe migraine with or without aura,
with time from onset to administration of study drug ≤4h. Efficacy was assessed using the Migraine
Patient Diary. The primary efficacy assessments included
• Response at 2, 3 and 4 h (percent of patients with headache improvement to mild or no pain at 2, 3 or 4 h post-dosing) and with no rescue medication before the relative time point.
• ≥ 2-point improvement response (percentage of patients with at least 2-point improvement in pain score from baseline and with no rescue medication before the relative timepoint)
• Pain-free rate (percentage of patients with no headache at 2, 3, and 4 h and with no rescue medication before the relative timepoint)
The secondary efficacy variables included:
• Sustained response rate (percentage of patients responders without rescue or recurrence from 4 to 24 h)
• Sustained pain-free rate (percentage of patients pain-free without rescue or recurrence from 4 to 24 h)
• Recurrence rate (percentage of patients with response who experience moderate or severe headache from 4 to 24 h)
• Non-pain efficacy measures such as relief of nausea, photophobia, or phonophobia at 2, 3 or 4 h (percentage of patients with no symptom at 2, 3, or 4 h, from a 2-3 baseline score).
Safety: Safety evaluation included collecting all AE sand SAEs, with their severity and relationship to
study drug, and pregnancies. They also included the regular monitoring of hematology, blood chemistry and urine performed at a central laboratory and regular assessments of vital signs, physical
condition and body weight.
Pharmacokinetic: The PK parameters were determined by non-compartmental method(s) using WinNonlin Pro (Version 5.2). The parameters determined were AUC0-2h, AUClast, Cmax, Tlag, Tmax,
T1/2 and others as appropriate.

Statistical Methods

Efficacy was assessed using the Migraine Patient Diary on Day 1. Response
rate was calculated for three treatment groups at all post-dose time points. Analysis with generalized

linear model (logit link function) was conducted at 2, 3 and 4 hour post-dose with treatment and time
as factors. Estimates and 90% confidence intervals for response rate of each treatment group at each
timepoint were provided together with odds ratio and their 90% confidence intervals for treatment
differences.
PoC was to be declared if, at interim (when 15 subjects in each treatment group complete the study),
the difference between response rate of BGG and response rate of Placebo was 35% (or more) at least at two time points out of the three specified time points (2h, 3h, 4h post-dose); or, at the end of
study evaluation, if the difference was 25% (or more) at least at two time points out of the three
specified time points.
Descriptive statistics of PK parameters included mean, SD, and CV, min and max. Geometric means
are presented as such. Since Tmax is generally evaluated by a nonparametric method, median values
and ranges were given for this parameter. All concentrations below the limit of quantification or missing
data were labeled as such in the concentration data listings. Concentrations below the Limit of
Quantification were treated as zero in summary statistics of concentration data and for calculation of PK parameters.

Study Population: Inclusion/Exclusion Criteria and Demographics

The main inclusion criteria included
・Patients with a diagnosis of migraine and who had experienced episodes of migraine, with or without aura (International Headache Society categories 1.1 and 1.2) for at least one year prior to
study entry, and experienced moderate or severe migraine.
・Patient who had more than one migraine episode but not more than 15 migraine days per month for each of the six months prior to the study.
・Patients who had used triptans in their past medical history.
・Patients who had migraine onset before 50 years of age.
The main exclusion criteria were
・Diagnosis of basilar, ophthalmologic or hemiplegic migraine.
・Experience of non-migraine headaches on more than 6 days per month in the past 6 months.
・Patients having taken any treatment for the migraine attack prior to arrival at the clinic for study
drug administration.
・Patients using migraine prophylactic treatments that interact with PGP (P-glycoprotein), medications that are potent inhibitors or inducers of CYP3A4 or interacting with PGP (P-glycoprotein), medications to improve intestinal motility that are PGP inhibitors,
・Patients using (or having used within one (1) week before initial dosing drugs that are contraindicated
for sumatriptan, such as ergotamine-containing or ergot-type medications (dihydroergotamine or methysergide); MAO-A inhibitors and SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline).
・Patients with the history of any psychiatric condition (e.g. depression and schizophrenia).

The sample size was based on primary objective of the study. In total, 75 patients (25 in each arm) were planned to be recruited with acute migraine in multiple study centers which are qualified for diagnosis and treatment of migraine.
The target population of 75 patients was enrolled as planned and none were discontinued from the study. All patients were analysed for safety and one patient in the BGG492 group was excluded from
the PD analysis set due to protocol deviation (mild severity of migraine at pre-dose). Twenty eight
patients were included in the PK analysis set.

Primary Objective Result(s)

Efficacy results The PoC criterion was not met as at the end of the treatment, the difference between responders to BGG492 treatment and placebo was below 25% at all three timepoints. However a positive and similar response compared to Sumatriptan was observed at “pain free” at all timepoints and “≥2 point improvement” at 4hrs. All three responses measured at 24hrs showed “sustained response”.

Pharmacokinetic results: Tmax (median 3 hr), Cmax and AUCs (AUC0-6h and AUC0-2h) for BGG492 in this study were consistent with data from the HV study CBGG492A2101. The inter-subject variability in Cmax and AUClast was moderate, except for AUC0-2h which was associated with significantly higher variability in this study compared to HV data, suggesting that the disease state may have affected initial absorption of BGG492.

Sumatriptan PK was comparable to published data for overencapsulated oral forms (Fuseau et al, 2001).

Safety Results

There were no deaths or AE related discontinuations in the study. Two patients in the BGG492 group experienced SAEs. The SAEs were mild in severity and resolved without requiring any intervention. Overall 49 (65.3 %) patients reported AEs during the study. The AEs observed in the study are consistent with the safety profile of BGG 492 (dizziness, vertigo and ataxia). The incidence of AEs was comparable in sumatriptan (56.0 %) and placebo (60.0 %) groups but was relatively higher in BGG492 (80.0 %) group. There was no meaningful change noted in any of the lab parameters and vital signs.

Overall BGG492 was safe and well tolerated in this study except for the two patients who experienced SAEs.

Other Relevant Findings

Not Applicable for this trial

Date of Clinical Trial Report

20-Jul-2011

Date Inclusion on Novartis Clinical Trial Results Database

24 Feb 2012

Date of Latest Update

9 Feb 2012