Sponsor

Novartis

Generic Drug Name

BGG492 (Selurampanel)

Trial Indication(s)

Chronic subjective tinnitus

Protocol Number

CBGG492A2210

Protocol Title

A multicenter, randomized, double-blind, placebo controlled, cross-over, proof of concept study comparing the effects of both single dose and repeated dosing treatment for 2 weeks of BGG492 in patients with chronic subjective tinnitus.

Clinical Trial Phase

Phase IIA

Phase of Drug Development

Phase II

Study Start/End Dates

First patient first visit: 27 Jan 2011
Last patient last visit: 31 Jan 2012

Reason for Termination (If applicable)

N/A

Study Design/Methodology

This was a multicenter, randomized, double-blind, placebo controlled, two-treatment period, cross-over study comparing the effects of both single and repeated dosing treatment of BGG492 for 2 weeks in patients with chronic subjective tinnitus. The study consisted of a 21-day screening period, two Baseline periods (one before each treatment period), two consecutive treatment periods separated by a single-blind placebo washout period. The second treatment period is followed by a safety observational period of consecutive 14 days which ends with the study completion evaluation day.

Centers

4 centers in 2 countries: Germany (3 centers) and The Netherlands (1 center).

Publication

Not planned yet.

Objectives:

The primary objective:

- To assess the multiple dose effects (including responder rates) of BGG492 after a 2-week treatment:
    a. On tinnitus loudness using a visual analogue scale (VAS)
    b. On the clinical status of tinnitus (patients' reaction to tinnitus) using the TBF-12 (Tinnitus Impairment Questionnaire).

The secondary objectives:

- To assess the effects of BGG492 both after single dose and a multiple dose 2-week treatment by the means of an audiological examination including audiometry, tinnitus matching, minimal masking level, and residual inhibition.
- To assess the effects of a single dose of BGG492 on tinnitus loudness and annoyance using VAS (current loudness and current annoyance).
- To assess the multiple dose effects of a 2-week treatment with BGG492 on tinnitus loudness (maximum loudness during last 24 hours) and tinnitus annoyance (current annoyance) using VAS.
- To assess safety and tolerability of BGG492 in patients with chronic subjective tinnitus.
- To determine the pharmacokinetic profile of BGG492 in patients with chronic subjective tinnitus and to explore the PK/PD relationship.

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

BGG492 50 mg hard gelatin capsules and matching placebo capsules for oral administration, TID regimen; two dose levels of BGG492, 100 mg and 50 mg TID.

Statistical Methods

- Efficacy

VAS (current tinnitus loudness) and TBF-12 responder rates were analyzed separately. They were summarized per treatment and over time. Summary statistics on responder rates included exact 90% confidence interval by Clopper and Pearson.

Percentage of responders was analyzed by generalized linear mixed model (logit link function, PROC GLIMMIX) with treatment (BGG492 or Placebo), sequence and period as fixed effects and patient as random effect. Estimation and 90% confidence interval of treatment difference (BGG492 vs Placebo) is provided.

For all composite scales such as TBF-12, if any of the answers was missing then the total score was set to missing. For patients who withdrew early, the data obtained after drop-out date was not included in analysis. The missing data was not imputed.

- Safety

All vital signs data are listed by treatment sequence, patient, and visit/time and if ranges were available abnormalities (and relevant orthostatic changes) are flagged. Summary statistics are provided by treatment and visit/time.

All ECG data are listed by treatment sequence, patient and visit/time, abnormalities are flagged. Summary statistics are provided by treatment and visit/time.

Abnormalities for QT (uncorrected) and QTcF intervals and abnormal changes from baseline were flagged in data listings. Findings on absolute values and changes to baseline are presented by treatment group, visit and timepoint.

All laboratory data are listed by treatment sequence, patient, and visit/time and abnormalities are flagged. Summary statistics are provided by treatment and visit/time.

All information obtained on adverse events is displayed by treatment sequence and patient.

The number and percentage of patients with adverse events are tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A patient with multiple adverse events within a body system is only counted once towards the total of this body system.

For the analysis by BGG492 dose level, an adverse event starting before a dose reduction and continuing into the lower dose timeframe in a period is counted only for the onset dose.

Adverse events that resulted in dose reduction to 50 mg TID or to permanent treatment discontinuation were summarized.

- Pharmacokinetics

Biofluid concentrations are expressed in ng/mL. All concentrations below the lower limit of quantification (LLOQ) or missing data are labeled as such in the concentration data listings. Concentrations below the limit of quantification have been treated as zero in summary statistics and for the calculation of PK Parameters.

Descriptive statistics of pharmacokinetic parameters included mean, SD, and CV, min and max. The geometric mean was identified when presented. A range of values were presented for selected variables. No inferential statistics were performed on PK Parameters.

Study Population: Key Inclusion/Exclusion Criteria

Study Population:

The main inclusion criteria

- Male and female patients, age 18 to 75 years (included)
- Diagnosed with THI severity grade 3, 4 or 5 (moderate, severe or catastrophic)
- Chronic (> 6 months and < 36 months) subjective tinnitus at Screening

The main exclusionary criteria

- Patients with diagnosis of intermittent or pulsatile tinnitus;
- Patients who had tinnitus as a concomitant symptom of a treatable otological disease, neurological tumors and/ temporo-mandibular joint disorders;
- Patients with diagnosed anxiety disorders, depression, schizophrenia or other significant psychiatric diseases requiring current drug treatment or required treatment in the previous 3 months for these diseases
- Patients with a cochlear implant.

Other protocol defined exclusion criteria were applicable

Participant Flow Table

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

	BGG492/Placebo N=48	Placebo/BGG492 N=48	Total N=96
Patients			
Randomized	48 (100.0%)	48 (100.0%)	96 (100.0%)
Completed	46 (95.8%)	44 (91.7%)	90 (93.8%)
Discontinued	2 (4.2%)	4 (8.3%)	6 (6.3%)
Patients received dose: 50 mg TID	28 (58.3%)	25 (52.1%)	53 (55.2%)
Patients received dose: 100 mg TID	20 (41.7%)	23 (47.9%)	43 (44.8%)
Completers treatment dosed 50 mg TID	26 (54.2%)	21 (43.8%)	47 (49.0%)
Completers treatment dosed 100 mg TID	15 (31.3%)	21 (43.8%)	36 (37.5%)
Completers treatment with lower dose 50 mg TID	3 (6.3%)	2 (4.2%)	5 (5.2%)
Completers study dosed 50 mg TID	28 (58.3%)	21 (43.8%)	49 (51.0%)
Completers study dosed 100 mg TID	15 (31.3%)	21 (43.8%)	36 (37.5%)
Completers study with lower dose 50 mg TID	3 (6.3%)	2 (4.2%)	5 (5.2%)
Included in Safety Population	48 (100.0%)	48 (100.0%)	96 (100.0%)
Included in PD Population	47 (97.9%)	45 (93.8%)	92 (95.8%)
Included in 2nd PD Population	47 (97.9%)	45 (93.8%)	92 (95.8%)
Included in ITT Population	48 (100.0%)	48 (100.0%)	96 (100.0%)

	BGG492/Placebo N=48	Placebo/BGG492 N=48	Total N=96
Main cause of discontinuation			
Adverse Event(s)	2 (4.2%)		2 (2.1%)
Subject withdrew consent		1 (2.1%)	1 (1.0%)
Protocol deviation		3 (6.3%)	3 (3.1%)

Baseline Characteristics

Demographic summary

		BGG492/Placebo N=48	Placebo/ BGG492 N=48	Total N=96
Age (years)	Mean (SD)	46.1 (13.48)	45.7 (13.73)	45.9 (13.53)
	Median	47.0	46.5	47.0
	Range	20 - 73	22 - 75	20 - 75
Gender - n(%)	Male	27 (56%)	29 (60%)	56 (58%)
	Female	21 (44%)	19 (40%)	40 (42%)
Predominant race - n(%)	Caucasian	46 (96%)	48 (100%)	94 (98%)
	Black	1 (2%)		1 (1%)
	Asian	1 (2%)		1 (1%)
Ethnicity - n (%)	Mixed Ethnicity	1 (2%)		1 (1%)

		BGG492/Placebo N=48	Placebo/ BGG492 N=48	Total N=96
	Other	47 (98%)	48 (100%)	95 (99%)
Height (cm)	Mean (SD)	172.61 (8.186)	175.42 (10.196)	174.02 (9.304)
	Median	173.00	177.00	174.00
	Range	153.0 - 190.0	154.0 - 195.0	153.0 - 195.0
Weight (kg)	Mean (SD)	74.21 (13.074)	81.28 (13.602)	77.75 (13.737)
	Median	71.90	80.00	76.10
	Range	51.9 - 99.5	50.3 - 114.8	50.3 - 114.8
BMI (kg/m2)	Mean (SD)	24.847 (3.5990)	26.380 (3.6032)	25.614 (3.6640)
	Median	25.100	25.715	25.510
	Range	18.17 - 30.80	19.02 - 32.83	18.17 - 32.83

Tinnitus Handicap Inventory (THI) summary

		BGG492/ Placebo N=48	Placebo/ BGG492 N=48	Total N=96
THI total score	Mean (SD)	58.4 (15.36)	53.7 (14.83)	56.0 (15.19)
	Median	57.0	50.0	54.0
	Range	38 - 94	36 - 92	36 - 94

		BGG492/ Placebo N=48	Placebo/ BGG492 N=48	Total N=96
THI grade - n (%)	2		2 (4%)	2 (2%)
	3	23 (48%)	30 (63%)	53 (55%)
	4	14 (29%)	10 (21%)	24 (25%)
	5	9 (19%)	5 (10%)	14 (15%)
	Missing	2 (4%)	1 (2%)	3 (3%)

Note: Only THI grade more than 2 (two) allowed the patient to be enrolled into the study. Total of two (2) patients were discontinued from the study due to the protocol deviation reported of THI severity grade 2 at the Screening.

Summary of Efficacy

Outcome measures

Primary Outcome Result(s)

Clinical status of tinnitus using TBF-12 after a 2-week treatment

Summary and Inference for responders in TBF-12 (0-24 points) (Pharmacodynamic analysis set)

	BGG492 TID (N=86)	Placebo (N=86)
Improvement of 3 points or more from baseline in TBF-12		
Response [N (%)]	32 (37.2)	23 (26.7)
90% CI* [%]	[28.50;46.60]	[19.02;35.71]
Comparison vs Placebo		
Odds Ratio (SE)**	1.62 (0.60)	

	BGG492 TID (N=86)	Placebo (N=86)
90% CI **	[0.89,2.93]	
p-value**	0.182	

* Exact 90% confidence interval by Clopper and Pearson

** Generalized linear mixed model with treatment, sequence and period as fixed and patient as random effect

Summary and Inference for responders in TBF-12 (0-24 points) - improve of 4 points or more (Pharmacodynamic analysis set)

	BGG492 TID (N=86)	**Placebo (N=86)**
Improvement of 4 points or more from baseline in TBF-12		
Response [N (%)]	23 (26.7)	12 (14.0)
90% CI* [%]	[19.02;35.71]	[8.25;21.63]
Comparison vs Placebo		
Odds Ratio (SE)**	2.30 (1.08)	
90% CI **	[1.10,4.83]	
p-value**	0.064	

* Exact 90% confidence interval by Clopper and Pearson

** Generalized linear mixed model with treatment, sequence and period as fixed and patient as random effect

Tinnitus loudness by VAS after a 2-week treatment

Summary and Inference for responders in current tinnitus loudness assessed by VAS (Pharmacodynamic analysis set)

	BGG492 TID (N=86)	**Placebo (N=87)**
Improvement of 10 mm or more from baseline in VAS		

	BGG492 TID (N=86)	Placebo (N=87)
Response [N (%)]	23 (26.7)	24 (27.6)
90% CI* [%]	[19.02;35.71]	[19.81;36.55]
Comparison vs Placebo		
Odds Ratio (SE)**	0.94 (0.34)	
90% CI **	[0.52,1.67]	
p-value**	0.848	

* Exact 90% confidence interval by Clopper and Pearson

** Generalized linear mixed model with treatment, sequence and period as fixed and patient as random effect

Secondary Outcome Result(s)

Tinnitus loudness and annoyance by VAS after single and multiple doses

Summary and Inference for responders in VAS after single dose (Pharmacodynamic analysis set)

Parameter: VAS Current Annoyance

	BGG492 TID (N=87)	Placebo (N=88)
Improvement of 10 mm or more from baseline in VAS		
Response [N (%)]	38 (43.7)	31 (35.2)
90% CI* [%]	[34.63;53.06]	[26.76;44.46]
Comparison vs Placebo		
Odds Ratio (SE)**	1.43 (0.46)	
90% CI **	[0.85,2.43]	
p-value**	0.256	

* Exact 90% confidence interval by Clopper and Pearson

** Generalized linear mixed model with treatment, sequence and period as fixed and patient as random effect

Summary and Inference for the other pharmacodynamic data (Pharmacodynamic analysis set)

Secondary Endpoints	Number of patient per treatment BGG492 | Placebo	Difference BGG492 vs placebo Adjusted* mean (SE)	90% CI	p-value**
Tinnitus loudness assessed by VAS (0-100 mm) after single dose	88|89	-5.13 (2.00)	(-8.46,-1.81)	0.012
Maximum tinnitus loudness during the last 24h assessed by VAS after multiple dose	85|87	-1.76 (1.83)	(-4.81,1.29)	0.340
Current annoyance by tinnitus assessed by VAS after single dose	87|88	-6.45 (2.18)	(-10.09,-2.82)	0.004
Current annoyance by tinnitus assessed by VAS after multiple dose	85|86	-2.42 (2.01)	(-5.77,0.93)	0.233

* Adjusted means are obtained by mixed effect model with period-wise baseline values as covariate and treatment, sequence, period and patient as fixed effect

** Unadjusted p-values for multiple testing

Effects of BGG492 by audiological measurements after single and multiple dose

Statistical analysis of audiological measurement (Pharmacodynamic analysis set)

	BGG492 (Lsmeans (SE) [90% CI])	Placebo (Lsmeans (SE) [90% CI])	(Diff (SE) [90% CI])	p-value
Loudness matching change from baseline*				
Day 1	1.14 (0.81) [-0.21,2.48]	0.88 (0.84) [-0.51,2.28]	0.25 (1.16) [-1.69,2.20]	0.827
Day 15	1.63 (1.32) [-0.56,3.82]	2.80 (1.32) [0.60,4.99]	-1.16 (1.87) [-4.27,1.95]	0.535
Minimal masking level change from baseline*				
Day 1	-1.98 (0.65) [-3.07,-0.90]	-2.44 (0.67) [-3.55,-1.33]	0.46 (0.93) [-1.10,2.01]	0.626
Day 15	-1.06 (1.16) [-3.00,0.87]	-0.38 (1.15) [-2.30,1.53]	-0.68 (1.64) [-3.40,2.05]	0.679
Pitch matching change from baseline*				
Day 1	-409.71 (240.85) [-810.89,-8.54	137.87 (245.06) [-270.33, 546.08	-547.58 (344.44) [-1121.33,26.1	0.116
Day 15	-27.24 (191.49) [-346.19,291.72	323.13 (189.14) [8.07,638.19]	-350.36 (269.67) [-799.56,98.83	0.198

Residual inhibition**				
Day 1	0.45 (0.06) [0.34,0.56]	0.42 (0.06) [0.32,0.53]	1.12 (0.38) [0.65,1.94]	0.727
Day 15	0.35 (0.06) [0.26,0.46]	0.38 (0.07) [0.28,0.50]	0.87 (0.31) [0.49,1.54]	0.687

*Adjusted means are obtained by fixed effect model with period-wise baseline values as covariate, treatment, sequence and period as fixed factors, and subject within sequence as fixed effect

**The percentage of patients with complete/partial inhibition is compared between treatments with a generalized linear mixed model with sequence, treatment and period as fixed effects and patient as random effect.

Summary of Safety

Adverse events - n (%) of subjects (Safety analysis set)

	BGG492 N=92 n (%)	Placebo N=94 n (%)	Total N=96 n (%)
Patients with AE(s)	63 (68.5%)	46 (48.9%)	74 (77.1%)
Dizziness	36 (39.1%)	9 (9.6%)	42 (43.8%)
Fatigue	19 (20.7%)	13 (13.8%)	31 (32.3%)
Headache	12 (13.0%)	18 (19.1%)	23 (24.0%)
Nasopharyngitis	11 (12.0%)	8 (8.5%)	18 (18.8%)
Increased appetite	11 (12.0%)	1 (1.1%)	12 (12.5%)
Inappropriate affect*	11 (12.0%)	1 (1.1%)	12 (12.5%)
Nausea	8 (8.7%)	4 (4.3%)	11 (11.5%)
Gait disturbance	8 (8.7%)	1 (1.1%)	9 (9.4%)
Vertigo	7 (7.6%)	3 (3.2%)	8 (8.3%)
Somnolence	7 (7.6%)	1 (1.1%)	8 (8.3%)
Vomiting	5 (5.4%)	2 (2.1%)	7 (7.3%)
Coordination abnormal	5 (5.4%)	2 (2.1%)	7 (7.3%)
Vision blurred	2 (2.2%)	4 (4.3%)	6 (6.3%)
Insomnia	3 (3.3%)	3 (3.2%)	6 (6.3%)

	BGG492 N=92 n (%)	Placebo N=94 n (%)	Total N=96 n (%)
Back pain	2 (2.2%)	4 (4.3%)	6 (6.3%)
Logorrhoea	5 (5.4%)	0	5 (5.2%)
Elevated mood	4 (4.3%)	1 (1.1%)	5 (5.2%)
Dysarthria	5 (5.4%)	0	5 (5.2%)
Autonomic nervous system imbalance	3 (3.3%)	2 (2.1%)	5 (5.2%)
Tinnitus	2 (2.2%)	2 (2.1%)	4 (4.2%)
Disturbance in attention	3 (3.3%)	1 (1.1%)	4 (4.2%)
Diarrhoea	2 (2.2%)	2 (2.1%)	4 (4.2%)
Urinary tract infection	1 (1.1%)	2 (2.1%)	3 (3.1%)
Rash	1 (1.1%)	2 (2.1%)	3 (3.1%)
Irritability	1 (1.1%)	2 (2.1%)	3 (3.1%)
Feeling drunk	3 (3.3%)	0	3 (3.1%)
Dry mouth	3 (3.3%)	1 (1.1%)	3 (3.1%)
Vestibular disorder	1 (1.1%)	1 (1.1%)	2 (2.1%)
Stupor	1 (1.1%)	1 (1.1%)	2 (2.1%)
Sleep disorder	1 (1.1%)	1 (1.1%)	2 (2.1%)
Pruritus	1 (1.1%)	1 (1.1%)	2 (2.1%)
Photosensitivity reaction	1 (1.1%)	1 (1.1%)	2 (2.1%)
Pain in extremity	2 (2.2%)	0	2 (2.1%)
Neck pain	2 (2.2%)	0	2 (2.1%)
Myalgia	1 (1.1%)	1 (1.1%)	2 (2.1%)
Libido increased	2 (2.2%)	0	2 (2.1%)
Hot flush	1 (1.1%)	1 (1.1%)	2 (2.1%)
Euphoric mood	2 (2.2%)	0	2 (2.1%)
Dysgeusia	1 (1.1%)	1 (1.1%)	2 (2.1%)
Decreased appetite	2 (2.2%)	0	2 (2.1%)
Balance disorder	2 (2.2%)	0	2 (2.1%)
Apathy	2 (2.2%)	0	2 (2.1%)

	BGG492 N=92 n (%)	Placebo N=94 n (%)	Total N=96 n (%)
Abdominal pain	2 (2.2%)	0	2 (2.1%)

Arranged by frequency in the total column
*Elation in all cases

Adverse events – n (%) of subjects, differentiated for dose groups (Safety analysis set)

	BGG492 100 mg TID N=42 n (%)	BGG492 50 mg TID N=54 n (%)	Placebo N=94 n (%)
Subjects with AE(s)	36 (85.7%)	31 (57.4%)	46 (48.9%)
Preferred term			
Dizziness	21 (50.0%)	17 (31.5%)	9 (9.6%)
Fatigue	13 (31.0%)	6 (11.1%)	13 (13.8%)
Inappropriate affect*	10 (23.8%)	1 (1.9%)	1 (1.1%)
Increased appetite	9 (21.4%)	2 (3.7%)	1 (1.1%)
Gait disturbance	8 (19.0%)	0	1 (1.1%)
Somnolence	7 (16.7%)	0	1 (1.1%)
Nausea	6 (14.3%)	2 (3.7%)	4 (4.3%)
Coordination abnormal	5 (11.9%)	0	2 (2.1%)
Dysarthria	5 (11.9%)	0	0
Headache	5 (11.9%)	8 (14.8%)	18 (19.1%)
Vomiting	5 (11.9%)	1 (1.9%)	2 (2.1%)

AEs ≥ 10% frequency, by preferred term and ranked by frequency observed in the 100 mg TID dose group
*Elation in all cases

Adverse events - brief summary (Safety analysis set)

	BGG492 100 mg TID N=42 n (%)	BGG492 50 mg TID N=54 n (%)	Placebo N=94 n (%)	Total N=96 n (%)
Patients with AE(s)	36 (85.7%)	31 (57.4%)	46 (48.9%)	74 (77.1%)
AEs of mild intensity	35 (83.3%)	29 (53.7%)	39 (41.5%)	70 (72.9%)
AEs of moderate intensity	17 (40.5%)	10 (18.5%)	14 (14.9%)	36 (37.5%)
AEs of severe intensity	2 (4.8%)	0	1 (1.1%)	3 (3.1%)
Study drug related	33 (78.6%)	29 (53.7%)	35 (37.2%)	71 (74.0%)
AEs leading to dose adjustment	4 (9.5%)	0	1 (1.1%)	5 (5.2%)
AEs leading to dose discontinuation	2 (4.8%)	0	0	2 (2.1%)
Serious AEs	0	0	1 (1.1%)	1 (1.0%)

Arranged by frequency in the total column

Other Relevant Findings

Summary statistics for PK parameters (Pharmacokinetic analysis set)

Compound: BGG492 , Matrix: Plasma , Analyte: BGG492			
		BGG492 50 mg TID	BGG492 100 mg TID
PK Parameters	**Statistic**		
Day: 1			
AUC0-4h (hr*ng/mL)	n	38	41
	Mean (SD)	4470 (1250)	7950 (2040)
	CV% mean	27.9	25.7
	Geo-mean	4310	7680
	CV% geo-mean	28.4	27.3
	Median	4240	7830
	(min/max)	2240 - 7550	4400 - 12200
Cmax (ng/mL)	n	39	41
	Mean (SD)	1950 (540)	3310 (970)
	CV% mean	27.7	29.3
	Geo-mean	1880	3180
	CV% geo-mean	28.7	29.4
	Median	1890	3160
	(min/max)	1000 - 3000	1850 - 5900
Tmax (hr)	n	39	41
	Median	2.00	3.00
	(min/max)	1.50 - 4.12	0.750 - 5.00
Day 15			
AUC0-4h (hr*ng/mL)	n	42	35
	Mean (SD)	4980 (1810)	8390 (3140)
	CV% mean	36.3	37.4
	Geo-mean	4490	6800
	CV% geo-mean	58.8	132.4

	Median	4810	8360
	(min/max)	461 - 8680	54.0 - 13800
Cmax (ng/mL)	n	42	35
	Mean (SD)	1990 (646)	3140 (1070)
	CV% mean	32.5	34.0
	Geo-mean	1850	2610
	CV% geo-mean	47.0	124.6
	Median	2010	3300
	(min/max)	284 - 3410	20.7 - 4870
Cmin (ng/mL)	n	42	35
	Mean (SD)	289 (254)	539 (381)
	CV% mean	87.9	70.8
	Geo-mean	214	431
	CV% geo-mean	118.9	89.0
	Median	243	453
	(min/max)	0.00 - 1410	0.00 - 1570
Tmax (hr)	n	42	35
	Median	2.00	2.02
	(min/max)	0.00 - 4.18	0.00 - 4.25

Date of Clinical Trial Report

08/January/2013

Date of Initial Inclusion on Novartis Clinical Trial Results website

30 Jun 2014

Date of Latest Update

Reason for Update