Abbreviated Novartis Clinical Trial Results Template

Sponsor

Novartis

Generic Drug Name

BGJ398

Trial Indication(s)

Advanced solid malignancies

Protocol Number

CBGJ398X1101

Protocol Title

A phase I study of oral BGJ398 in Asian patients with advanced solid tumor having alterations of the FGF-R pathway

Clinical Trial Phase

Phase of Drug Development

Phase II

Study Start/End Dates

19 Oct 2012 (first patient first visit) to 07 Feb 2019 (last patient last visit)

Reason for Termination

Novartis terminated the study based on the sponsor's reason.

Study Design/Methodology

This was a multi-center, open label, dose finding, phase I study of oral single agent BGJ398, administered on a continuous once and/or twice daily (q.d. and/or b.i.d.) schedule in patients with advanced solid tumor for which no further standard therapy exists. This study was consisted of 3 parts: dose escalation part, safety run-in part for Chinese patients, dose expansion part. Tumors had to harbor an amplification of the FGF-R1, the FGF-R2, or a mutation of the FGF-R3 gene, or other FGF-R alteration. The study began with a dose-escalation part in which successive cohorts of newly enrolled patients received increasing doses of BGJ398 (50 mg q.d., 100 mg q.d.) on a once daily schedule in a 28-day cycle until the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) was determined.

Centers

8 centers in 2 countries: Japan (5), China (3)

Objectives:

Primary objective: To estimate the MTD and/or RDE and schedule of the single agent oral BGJ398 in Japanese patients with advanced solid tumors.

Secondary objectives:

- To characterize the safety and tolerability of oral BGJ398 in Asian (Japanese and Chinese) patients.
- To determine the pharmacokinetic (PK) profiles of oral BGJ398 including known pharmacologically active metabolites BHS697, BQR917 and CQM157 in Asian patients.
- To assess any preliminary anti-tumor activity of BGJ398 in Asian patients.

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

BGJ398 capsules for oral administration were provided at dosage strengths of 5 mg, 25 mg, and 100 mg.

Statistical Methods

Patient population: The full analysis set (FAS) included all patients who received at least one dose of BGJ398 and was used for all analyses. The *safety set* included all patients who received at least one dose of BGJ398 and had at least one valid post-baseline safety assessment. The dose determining set (DDS) included all patients from the safety set who either completed a minimum exposure requirement and had sufficient safety evaluations or had a dose limiting toxicity (DLT) during the first cycle. The PK analysis set (PAS) consisted of all patients in FAS who had at least one blood sample providing evaluable PK data for BGJ398 or the metabolites.

MTD: The primary variable of the study was the incidence rate and category of DLT during the Cycle 1. Estimation of the MTD in the dose escalation part of the study was based upon the estimation of the probability of DLT in Cycle 1 for patients in the DDS. Two 2-parameter adaptive Bayesian logistic regression models (BLRM1 and BLRM2) guided by the EWOC principle were used during the dose escalation part for BGJ398 for recommendation of MTD of BGJ398. The model 1 (BLRM1) estimated the BGJ398 doses (total) - outcome A DLT mechanism and the model 2 (BLRM2) estimated the relationship between the BGJ398 doses (total) and any DLT (outcome A or B). The MTD was defined to be the highest dose of BGJ398 given for at least 21 days in the first treatment cycle (28 days) in which it is expected to produce medically unacceptable DLT of any type in less than 33% of the patients (outcome B), or producing specific medically unacceptable DLT in less than 15% of the patients (outcome A). DLTs were listed for patients in the DDS.

Efficacy: Preliminary anti-tumor activity was assessed using the investigator tumor assessments evaluated under RECIST v 1.1. Best overall response (BOR), overall response rate (ORR) and progression-free survival (PFS) were assessed. BOR for each patient and individual lesion measurements were listed. ORR was the proportion of patients with a BOR of complete response (CR) or partial response (PR).

Safety: The safety summary tables included only on-treatment assessments (from day of start of study treatment to no later than 28 days following the last date of study treatment) and were presented by treatment group and for all patients. All safety assessments were listed. Laboratory tests (hematology, biochemistry, coagulation, urinalysis) were listed for all parameters and treatment groups. Data from other safety assessments (pregnancy test and corneal pachymetry) were listed by patient and treatment group.

Pharmacokinetics: The PK parameters were analyzed using descriptive statistics per treatment group for dose escalation part and safety run-in part for Chinese patients. When a geometric mean was presented, it was stated as such. Tmax was generally evaluated by a nonparametric method, median values and ranges were presented for this parameter.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria

- Patients of either sex and ≥ 18 years of age.
- Dose escalation part: Japanese patients with histologically/cytologically confirmed advanced solid tumors with FGF-R1 or FGF-R2 amplification, FGF-R3 mutation or other FGF-R alteration, for which no further effective standard anti-cancer therapy existed. Safety run-in part for Chinese patients: Chinese patients with histologically/cytologically confirmed advanced solid tumors with FGF-R1 or FGF-R2 amplification, FGF-R3 mutation, or other FGF-R alteration for which no further effective standard anti-cancer therapy existed. Dose expansion part: Asian (Japanese and Chinese) patients with histologically/cytologically confirmed lung squamous cell carcinoma with FGF-R1 amplification, for which no further effective standard anti-cancer therapy existed.
- Measurable or non-measurable (but evaluable) disease as determined by Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.
- ECOG performance status 0-2.
- Adequate bone marrow function.
- Adequate hepatic and renal function.
- Adequate calcium-phosphate homeostasis.
- Adequate cardiovascular function

Key exclusion criteria

- Patients with primary central nervous system (CNS) tumor or CNS tumor involvement
- Patients with history and/or current evidence of endocrine alteration of calcium/phosphate homeostasis
- History and/or current evidence of clinically significant ectopic mineralization/calcification
- Current evidence of corneal disorder/keratopathy
- Use of medications that are known to prolong the QT interval or are associated with risk of Torsades de Pointes
- Clinically significant cardiac disease or impaired cardiac function
- Patients who received systemic anti-cancer treatment prior to the first dose of BGJ398 within protocol defined timelines

Prior radio therapy that includes > 30% of bone marrow reserve.

Participant Flow Table

Patient disposition by treatment (Full analysis set)

	50 mg q.d. (Japanese patients) N = 4 n (%)	100 mg q.d. (Japanese patients) N = 2 n (%)	Total (Japanese patients) N = 6 n (%)	100 mg q.d. (Chinese p atients) N = 3 n (%)	All patients N = 9 n (%)
Patients <enrolled>					
Untreated	0	0	0	0	0
Treated	4 (100)	2 (100)	6 (100)	3 (100)	9 (100)
Patients treated					
Treatment ongoing	0	0	0	0	0
End of treatment	4 (100)	2 (100)	6 (100)	3 (100)	9 (100)
Primary reason for end of treatment					
Adverse event	0	2 (100)	2 (33.3)	1 (33.3)	3 (33.3)
Progressive disease	3 (75.0)	0	3 (50.0)	2 (66.7)	5 (55.6)
Study terminated by sponsor	1 (25.0)	0	1 (16.7)	0	1 (11.1)
Study evaluation after end of treatment					
Patients no longer being followed for study evaluation	3 (75.0)	2 (100)	5 (83.3)	3 (100)	8 (88.9)
Patients continuing to be followed for study evaluation	0	0	0	0	0
Primary reason for study evaluation completion					
Completed	2 (50.0)	1 (50.0)	3 (50.0)	0	3 (33.3)
Adverse event	0	1 (50.0)	1 (16.7)	0	1 (11.1)
Progressive disease	0	0	0	2 (66.7)	2 (22.2)
New therapy for study indication	1 (25.0)	0	1 (16.7)	1 (33.3)	2 (22.2)

Study evaluation completion corresponds to the evaluation performed 28-day following treatment discontinuation.

Baseline Characteristics

Demographics by treatment dose –escalation part (Full analysis set)

Demographics Variable	50 mg q.d. (Japanese patients) N = 4	100 mg q.d. (Japanese patients) N = 2	Total (Japanese patients) N = 6	100 mg q.d. (Chinese patients) N = 3	All patients N = 9
Age (years)					
n	4	2	6	3	9
Mean	53.3	63.0	56.5	56.3	56.4
SD	19.00	0.00	15.55	7.64	12.88
Median	61.0	63.0	62.5	58.0	62.0
Minimum	25	63	25	48	25
Maximum	66	63	66	63	66
Age category (years) -n (%)					
<65	3 (75.0)	2 (100)	5 (83.3)	3 (100)	8 (88.9)
>=65	1 (25.0)	0	1 (16.7)	0	1 (11.1)
Sex -n (%)					
Female	1 (25.0)	0	1 (16.7)	0	1 (11.1)
Male	3 (75.0)	2 (100)	5 (83.3)	3 (100)	8 (88.9)
Race -n (%)					
Asian	4 (100)	2 (100)	6 (100)	3 (100)	9 (100)
Ethnicity -n (%)					
Chinese	0	0	0	3 (100)	3 (33.3)
Japanese	4 (100)	2 (100)	6 (100)	0	6 (66.7)

Demographics Variable	50 mg q.d. (Japanese patients) N = 4	100 mg q.d. (Japanese patients) N = 2	Total (Japanese patients) N = 6	100 mg q.d. (Chinese patients) N = 3	All patients N = 9
Weight (kg)					
n	4	2	6	3	9
Mean	72.0	69.5	71.2	53.7	65.3
SD	16.12	4.95	12.75	9.61	14.18
Median	74.9	69.5	70.8	52.0	66.0
Minimum	51	66	51	45	45
Maximum	87	73	87	64	87
Height (cm)					
n	4	2	6	3	9
Mean	166.8	170.0	167.8	164.0	166.5
SD	8.95	1.91	7.17	6.56	6.82
Median	170.0	170.0	170.0	165.0	168.6
Minimum	154	169	154	157	154
Maximum	173	171	173	170	173
ECOG performance status -n (%)					
0	1 (25.0)	2 (100)	3 (50.0)	0	3 (33.3)
1	3 (75.0)	0	3 (50.0)	3 (100)	6 (66.7)

SD: standard deviation

Summary of Efficacy

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Summary of best overall response by treatment as per investigator (Full analysis set)

	50 mg q.d. (Japanese patients) N = 4 n (%)	100 mg q.d. (Japanese patients) N = 2 n (%)	Total (Japanese patients) N = 6 n (%)	100 mg q.d. (Chinese patients) N = 3 n (%)	ALL patients N = 9 n (%)
Best overall response					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	0	0	0	0	0
Non-Complete response/Non-Progressive disease (Non-CR/Non-PD)	0	0	0	0	0
Stable disease (SD)	3 (75.0)	1 (50.0)	4 (66.7)	0	4 (44.4)
Progressive disease (PD)	1 (25.0)	1 (50.0)	2 (33.3)	3 (100)	5 (55.6)
Overall response rate (ORR)					
(CR or PR)	0	0	0	0	0
95% CI	(0.0 - 60.2)	(0.0 - 84.2)	(0.0 - 45.9)	(0.0 - 70.8)	(0.0 - 33.6)
Disease control rate (DCR)					
(CR or PR or Non-CR/Non-PD or SD)	3 (75.0)	1 (50.0)	4 (66.7)	0	4 (44.4)
95% CI	(19.4 - 99.4)	(1.3 - 98.7)	(22.3 - 95.7)	(0.0 - 70.8)	(13.7 - 78.8)

The exact binomial 95% CI for ORR and DCR were computed.

Summary of primary PK parameters for BGJ398 by treatment (Pharmacokinetic analysis set) Profile day: CYCLE 1 DAY 1

Treatment	Statistics	AUC0-24h (hr*ng/mL)	AUCinf (hr*ng/mL)	AUClast (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
50 mg qd (Japanese patients) (N = 4)	n	4	3	4	4	4	3
	Mean (SD)	221 (200)	282 (215)	208 (207)	52.5 (47.7)	NA	3.53 (2.13)
	CV% mean	90.4	76.3	99.5	90.8	NA	60.5
	Geo-mean	155	228	132	34.1	NA	3.13
	CV% Geo-mean	136.1	98.3	175.5	178.0	NA	65.4
	Median	171	226	151	43.5	2.48	2.85
	[Min; Max]	[46.0; 498]	[100; 520]	[30.4; 498]	[7.28; 116]	[2.00; 3.00]	[1.81; 5.92]
100 mg qd (Japanese patients) (N = 2)	n	2	2	2	2	2	2
	Mean (SD)	688 (122)	720 (143)	685 (117)	100 (5.59)	NA	4.73 (0.669)
	CV% mean	17.7	19.8	17.1	5.6	NA	14.2
	Geo-mean	683	713	680	100	NA	4.70
	CV% Geo-mean	17.9	20.1	17.4	5.6	NA	14.3
	Median	688	720	685	100	3.50	4.73
	[Min; Max]	[602; 774]	[619; 820]	[602; 768]	[96.1; 104]	[2.90; 4.10]	[4.25; 5.20]
100 mg qd (Chinese patients) (N = 3)	n	3	2	3	3	3	2
	Mean (SD)	485 (116)	565 (85.1)	413 (230)	65.6 (41.4)	NA	5.32 (1.28)
	CV% mean	23.9	15.0	55.7	63.1	NA	24.1

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Treatment	Statistics	AUC0-24h (hr*ng/mL)	AUCinf (hr*ng/mL)	AUClast (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
	Geo-mean	476	562	357	55.1	NA	5.24
	CV% Geo-mean	24.5	15.2	81.8	91.2	NA	24.7
	Median	476	565	476	67.6	3.00	5.32
	[Min; Max]	[374; 605]	[505; 625]	[158; 605]	[23.3; 106]	[2.00; 4.00]	[4.42; 6.22]

n: number of patients with non-missing values.

CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of primary PK parameters for BGJ398 by treatment (Pharmacokinetic analysis set) Profile day: CYCLE 1 DAY 15

Treatment	Statistics	AUC0-24h (hr*ng/mL)	AUCinf (hr*ng/mL)	AUClast (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
50 mg qd (Japanese patients) (N = 4)	n	3	NA	4	4	4	3
	Mean (SD)	1120 (1410)	NA	841 (1290)	85.1 (110)	NA	7.11 (5.23)
	CV% mean	125.9	NA	152.9	129.7	NA	73.5
	Geo-mean	526	NA	213	28.8	NA	6.02
	CV% Geo-mean	378.8	NA	1085.7	806.6	NA	77.3
	Median	531	NA	303	47.7	3.48	4.58
	[Min; Max]	[100; 2730]	NA	[18.8; 2740]	[2.16; 243]	[2.03; 8.00]	[3.63; 13.1]
100 mg qd (Japanese patients) (N = 2)	n	1	NA	1	1	1	1
	Mean (SD)	1620 (-)	NA	1620 (-)	236 (-)	NA	8.99 (-)
	CV% mean	NA	NA	NA	NA	NA	NA
	Geo-mean	1620	NA	1620	236	NA	8.99
	CV% Geo-mean	NA	NA	NA	NA	NA	NA

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Treatment	Statistics	AUC0-24h (hr*ng/mL)	AUCinf (hr*ng/mL)	AUClast (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
	Median	1620	NA	1620	236	2.97	8.99
	[Min; Max]	[1620; 1620]	NA	[1620; 1620]	[236; 236]	[2.97; 2.97]	[8.99; 8.99]
100 mg qd (Chinese patients) (N = 3)	n	2	NA	3	3	3	2
	Mean (SD)	1660 (616)	NA	2310 (1210)	162 (38.2)	NA	10.5 (1.21)
	CV% mean	37.2	NA	52.6	23.6	NA	11.5
	Geo-mean	1600	NA	2100	159	NA	10.5
	CV% Geo-mean	39.5	NA	58.5	26.1	NA	11.6
	Median	1660	NA	2080	182	3.90	10.5
	[Min; Max]	[1220; 2090]	NA	[1220; 3620]	[118; 186]	[3.00; 10.20]	[9.66; 11.4]

n: number of patients with non-missing values.

CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of primary PK parameters for BGJ398 by treatment (Pharmacokinetic analysis set) Profile day: CYCLE 1 DAY 28

Treatment	Statistics	AUC0-24h (hr*ng/mL)	AUCinf (hr*ng/mL)	AUClast (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
50 mg qd (Japanese patients) (N = 4)	n	3	NA	3	3	3	3
	Mean (SD)	201 (122)	NA	189 (132)	30.6 (23.9)	NA	5.22 (2.25)
	CV% mean	61.0	NA	69.5	78.2	NA	43.2
	Geo-mean	179	NA	164	25.1	NA	4.88
	CV% Geo-mean	61.2	NA	71.1	88.4	NA	48.3
	Median	140	NA	120	20.8	2.95	5.12
	[Min; Max]	[120; 342]	NA	[107; 341]	[13.1; 57.8]	[2.00; 3.00]	[3.02; 7.52]

FRM-7043019 version 3.0

Treatment	Statistics	AUC0-24h (hr*ng/mL)	AUCinf (hr*ng/mL)	AUClast (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
100 mg qd (Japanese patients) (N = 2)	n	1	NA	1	1	1	1
	Mean (SD)	1860 (-)	NA	1840 (-)	113 (-)	NA	14.3 (-)
	CV% mean	NA	NA	NA	NA	NA	NA
	Geo-mean	1860	NA	1840	113	NA	14.3
	CV% Geo-mean	NA	NA	NA	NA	NA	NA
	Median	1860	NA	1840	113	6.02	14.3
	[Min; Max]	[1860; 1860]	NA	[1840; 1840]	[113; 113]	[6.02; 6.02]	[14.3; 14.3]
100 mg qd (Chinese patients) (N = 3)	n	1	NA	1	1	1	1
	Mean (SD)	1400 (-)	NA	1390 (-)	168 (-)	NA	9.66 (-)
	CV% mean	NA	NA	NA	NA	NA	NA
	Geo-mean	1400	NA	1390	168	NA	9.66
	CV% Geo-mean	NA	NA	NA	NA	NA	NA
	Median	1400	NA	1390	168	2.97	9.66
	[Min; Max]	[1400; 1400]	NA	[1390; 1390]	[168; 168]	[2.97; 2.97]	[9.66; 9.66]

n: number of patients with non-missing values.

CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of Safety

Safety Results

In this study, MTD and RDE could not be determined due to the study termination by sponsor's reason.

- There were no patients in the DDS who experienced DLT during the first 28 days of treatment.
- No on-treatment deaths were reported in this study.

Adverse events in more than or equal to 2 patients (20%) of all patients, regardless of study drug relationship, by preferred term, maximum grade and treatment (Safety set)

	50 mg q.d. (Japanese patients) N = 4		100 mg q.d. (Japanese patients) N = 2		Total (Japanese patients) N = 6		100 mg q.d. (Chinese patients) N = 3		All patients N = 9	
Preferred term	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
-Total	4 (100)	3 (75.0)	2 (100)	0	6 (100)	3 (50.0)	3 (100)	1 (33.3)	9 (100)	4 (44.4)
Alanine aminotransferase increased	2 (50.0)	0	1 (50.0)	0	3 (50.0)	0	2 (66.7)	0	5 (55.6)	0
Aspartate aminotransferase increased	1 (25.0)	0	1 (50.0)	0	2 (33.3)	0	2 (66.7)	0	4 (44.4)	0
Hyperphosphataemia	2 (50.0)	0	2 (100)	0	4 (66.7)	0	0	0	4 (44.4)	0
Anaemia	2 (50.0)	1 (25.0)	0	0	2 (33.3)	1 (16.7)	1 (33.3)	0	3 (33.3)	1 (11.1)
Blood phosphorus increased	0	0	0	0	0	0	3 (100)	0	3 (33.3)	0
Cancer pain	3 (75.0)	1 (25.0)	0	0	3 (50.0)	1 (16.7)	0	0	3 (33.3)	1 (11.1)
Constipation	1 (25.0)	0	2 (100)	0	3 (50.0)	0	0	0	3 (33.3)	0
Dry eye	2 (50.0)	0	1 (50.0)	0	3 (50.0)	0	0	0	3 (33.3)	0

	50 mg q.d. (Japanese patients) N = 4		100 mg q.d. (Japanese patients) N = 2		Total (Japanese patients) N = 6		100 mg q.d. (Chinese patients) N = 3		All patients N = 9	
Preferred term	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Alopecia	1 (25.0)	0	1 (50.0)	0	2 (33.3)	0	0	0	2 (22.2)	0
Decreased appetite	2 (50.0)	0	0	0	2 (33.3)	0	0	0	2 (22.2)	0
Dyspnoea	2 (50.0)	1 (25.0)	0	0	2 (33.3)	1 (16.7)	0	0	2 (22.2)	1 (11.1)
Hypertension	2 (50.0)	2 (50.0)	0	0	2 (33.3)	2 (33.3)	0	0	2 (22.2)	2 (22.2)
Hyponatraemia	1 (25.0)	1 (25.0)	0	0	1 (16.7)	1 (16.7)	1 (33.3)	0	2 (22.2)	1 (11.1)
Hypoproteinaemia	0	0	0	0	0	0	2 (66.7)	0	2 (22.2)	0
Nausea	2 (50.0)	0	0	0	2 (33.3)	0	0	0	2 (22.2)	0
Punctate keratitis	0	0	2 (100)	0	2 (33.3)	0	0	0	2 (22.2)	0
Pyrexia	2 (50.0)	0	0	0	2 (33.3)	0	0	0	2 (22.2)	0
Vomiting	2 (50.0)	0	0	0	2 (33.3)	0	0	0	2 (22.2)	0
Weight decreased	2 (50.0)	0	0	0	2 (33.3)	0	0	0	2 (22.2)	0

Other Relevant Findings

Not applicable

Conclusion:

- Overall, BGJ398 at all dose levels administered demonstrated that AEs were mild to moderate, manageable, and reversible in Asian (Japanese and Chinese) patients.

- MTD and RDE for Japanese patients could not be determined due to the study termination by sponsor's reason.

Date of Clinical Trial Report

26 Sep 2019