Full Novartis Clinical Trial Results Template

Sponsor

Novartis

Generic Drug Name

BGJ398 / BYL719 (Alpelisib)

Trial Indication(s)

Advanced solid tumors

Protocol Number

BGJ398X2102

Protocol Title

A Phase Ib, open-label study of oral BGJ398 in combination with oral BYL719 in adult patients with select advanced solid tumors

Clinical Trial Phase

Ib

Phase of Drug Development

I

Study Start/End Dates

02-Oct-2013 to 23-Aug-2016

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This multi-center, open-label Phase Ib dose-escalation study was designed to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of the combination of oral BGJ398 with oral BYL719. Upon identification of the MTD and/or RDE, an expansion part was opened to patient enrollment to further characterize the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of the combination.

Approximately 15 patients with advanced solid cancers with PIK3CA mutations were anticipated to be treated in the dose-escalation part. Upon identification of the MTD and/or RDE, approximately 35 patients with advanced solid cancers (except colorectal cancer (CRC)) with PIK3CA mutations with or without FGFR mutations, amplifications, or translocations were anticipated to be treated in the expansion part. Treatment in both parts was administered in 28-day cycles.

To enter the screening phase of the study, patients must have had written documentation of the required molecular alterations. The screening period began once the patient had signed the study informed consent. All screening evaluations were required to be performed before study treatment administration began.

The treatment period began on Cycle 1, Day 1 and continued in 28-day cycles until disease progression, start of new anti-tumor cancer therapy, failure to comply with study requirements, unacceptable toxicity, withdrawal of informed consent, death, and/or at the discretion of the investigator or sponsor.

The End of treatment (EOT) visit was to occur within 14 days after last administration of study treatment. All participating patients were required to complete this visit even if they had discontinued prematurely.

At minimum patients were required to complete the safety follow-up assessments 30 days after the last dose of the study treatment.

Centers

Twenty-two centers in 12 countries: United States (7), Spain (3), France (2), Italy (2), Australia (1), Belgium (1), Canada (1), Germany (1), Netherlands (1), Republic of Korea (1), Singapore (1) and Switzerland (1)

Objectives:

Primary objective:

•To determine the MTD and/or RDE of BGJ398 in combination with BYL719

Secondary objectives:

•To characterize the safety and tolerability of BGJ398 in combination with BYL719 at the MTD and/or RDE.

•To determine the single- and multiple-dose PK profiles of the investigational drugs in combination (BGJ398 and BYL719).

•To assess any preliminary antitumor activity of the combination of BGJ398 and BYL719.

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

BGJ398 hard gelatin capsules for oral use were supplied to the investigators at dosage strengths of 5 mg, 25 mg, 100 mg, and 120 mg. BYL719 film-coated tablets for oral use were supplied at dosage strengths of 10 mg, 50 mg, and 200 mg. Patients received BYL719 once daily continuously and BGJ398 once daily for the first 21 days of the 28-day cycle followed by a 7-day (1-week) break.

Statistical Methods

All data were analyzed by the Sponsor. SAS® version 9.4 was used in all analyses other than Bayesian analyses. The Bayesian modeling of the dose-toxicity relationship used for dose-escalation decision making and inference for the MTD was performed using internal Novartis R library functions (OncoBayes) created by Novartis's Methodology group and was run using R version 3-2.3 in MODESIM/GPSII environment.

An adaptive BLRM guided by the escalation with overdose control (EWOC) principle was used to guide the dose escalation up to the declaration of MTD/RDE. A 5-parameter BLRM for combination treatment was fitted on the dose-limiting toxicity data (i.e. absence or presence of DLT) accumulated throughout the dose-escalation part for modeling the dose-DLT relationship of BGJ398 and BYL719 when given in combination.

Dose recommendations were based on posterior summaries for each dose, primarily the posterior probabilities for the following three (3) intervals:

1. [0, 16%) under-dosing
2. [16%, 35%) targeted toxicity

3. [35%, 100%] excessive/unacceptable toxicity

Following the principle of EWOC, after each cohort of patients the recommended dose was the one with the highest posterior probability of the DLT rate falling in the target interval [16%, 35%) among the doses fulfilling EWOC, such that it was unlikely (<25% posterior probability) that the DLT rate at the dose was either excessively or unacceptably toxic (DLT rate ≥ 35%).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Patients eligible for inclusion in this study had to meet all of the following criteria:

- Patients with histologically/cytologically confirmed advanced or metastatic solid tumors who have failed standard therapy or for whom no effective standard anti-cancer therapy exists
    - Dose-escalation and dose-expansion parts: Any solid tumor with written documentation of local or central laboratory determination of PIK3CA gene mutation
    - Dose-expansion part: Any solid tumor with written documentation of local or central laboratory determination of alterations to FGFR1, FGFR2, or FGFR3 (mutations, amplifications, translocations), as appropriate for the arm in which the patient was enrolled. One arm of the expansion part was to exclusively enroll patients with metastatic breast cancer. Patients with a diagnosis of CRC were to be excluded from the expansion part.
- A representative tumor sample was available for molecular testing, unless agreed upon between Novartis and the Investigator.
- Evidence of measurable or evaluable disease, as determined by RECIST v1.1
- Patients ≥ 18 years of age of either gender
- ECOG/WHO performance status of 0-2
- Able to read and/or understand the details of the study and provide written evidence of informed consents as approved by Institutional Review Board/Ethics Committee.

Exclusion criteria

The main exclusion criteria were:

- For patients enrolled in dose expansion at MTD/RDE, previous treatment with either a selective FGFR inhibitor, PI3K inhibitor, or MEK inhibitor. (In exceptional situations, prior treatment with a PI3K inhibitor may be allowed if agreed to by the Sponsor based on discussion with the Investigator)
- History of another primary malignancy except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin or any other curatively treated malignancy that has not been treated in the prior 3 months or expected to require treatment for recurrence during the course of the study
- Patients with primary central nervous system tumors. Secondary (metastatic) central nervous system tumors are allowed provided that they are clinically stable for a period of 30 days prior to study entry and there is not a requirement for steroid or anti-convulsant therapy.
- Patients with diabetes mellitus requiring insulin treatment and/or with clinical signs or with fasting glucose ≥ 140 mg/dL / 7.8 mmol/L, history of clinically significant gestational diabetes mellitus or documented steroid-induced diabetes mellitus
- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BGJ398 or BYL719 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection)
- History and/or current evidence of endocrine alterations of calcium/phosphate homeostasis, e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis, etc.
- Treatment with any of the following anti-cancer therapies prior to the first dose of the combination of BGJ398 and BYL719 within the stated timeframes
    - Cyclical chemotherapy (intravenous) within a period of time that is shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C)
    - Biological therapy (e.g., antibodies) within a period of time that is ≤ 5 t1/2 or ≤ 4 weeks, whichever is shorter, prior to starting study drug
    - Continuous or intermittent small molecule therapeutics within a period of time that is ≤ 5 t1/2 or ≤ 4 weeks (whichever is shorter) prior to starting study drug
    - Any other investigational agents within a period of time that is ≤ 5 t1/2 or less than the cycle length used for that treatment or ≤ 4 weeks (whichever is shortest) prior to starting study drug
    - Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug

- Insufficient bone marrow function
    - Absolute neutrophil count <1000/mm3 [1.0 × 109/L]
    - Platelets <75000/mm3 [75 × 109/L]
    - Hemoglobin <9.0 g/dL
- Insufficient hepatic and renal function
    - Total bilirubin >1.5× upper limit of normal (ULN)
    - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) or Alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) >3× ULN (AST or ALT >5× ULN in the presence of liver metastases)
    - Serum creatinine >1.5 ULN and a calculated or measured creatinine clearance <45 cc/min
- Calcium-phosphate homeostasis
    - phosphorus outside of normal limits
    - Total (or corrected total calcium) and ionized serum calcium outside of normal limits
- Clinically significant cardiac disease including any of the following:
    - Congestive heart failure requiring treatment (New York Heart Association grade ≥ 2), left ventricular ejection fraction (LVEF) <50% as determined by Multi gated acquisition scan (MUGA) scan or Echocardiogram (ECHO), or uncontrolled hypertension (refer to WHO-ISH guidelines)
    - History or presence of clinically significant ventricular arrhythmias, atrial fibrillation, resting bradycardia, or conduction abnormality
    - Unstable angina pectoris or acute myocardial infarction ≤ 3 months prior to starting study drug
    - Corrected QT interval using Fredericia's formula (QTcF) >450 msec
    - History of congenital long QT syndrome
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months following the discontinuation of study treatment. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to Screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
- Combination of the following (a+b):

  a. Placement of an intrauterine device or intrauterine system

  b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

Oral contraceptives, injected or implanted hormonal methods are not allowed as the sole method of contraception because neither BGJ398 nor BYL719 have been characterized with respect to their potential to interfere with PK and/or the effectiveness of oral contraceptives.

Post-menopausal women are allowed to participate in this study. Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child-bearing potential.

Participant Flow Table

Patient disposition by treatment (Full Analysis Set)

Disposition Reason	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
Patients treated								

Disposition Reason	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
Treatment discontinued	4 (100)	4 (100)	6 (100)	6 (100)	5 (100)	6 (100)	31 (100)	62 (100)
Primary reason for end of treatment								
ADVERSE EVENT	1 (25.0)	0	0	1 (16.7)	1 (20.0)	1 (16.7)	4 (12.9)	8 (12.9)
PROGRESSIVE DISEASE	3 (75.0)	4 (100.0)	6 (100.0)	4 (66.7)	3 (60.0)	5 (83.3)	23 (74.2)	48 (77.4)
PROTOCOL DEVIATION	0	0	0	0	0	0	1 (3.2)	1 (1.6)
SUBJECT/GUARDIAN DECISION	0	0	0	1 (16.7)	1 (20.0)	0	3 (9.7)	5 (8.1)
Primary reason for study evaluation completion								
COMPLETED	4 (100.0)	1 (25.0)	3 (50.0)	2 (33.3)	3 (60.0)	2 (33.3)	5 (16.1)	20 (32.3)
DEATH	0	0	2 (33.3)	0	0	0	3 (9.7)	5 (8.1)
NEW THERAPY FOR STUDY INDICATION	0	3 (75.0)	0	1 (16.7)	0	1 (16.7)	1 (3.2)	6 (9.7)
PROGRESSIVE DISEASE	0	0	0	0	0	0	4 (12.9)	4 (6.5)
PROTOCOL DEVIATION	0	0	0	0	0	0	1 (3.2)	1 (1.6)

- Study evaluation completion corresponds to the evaluation performed 30-day following treatment discontinuation.

Baseline Characteristics

Demographics by treatment (Full analysis set)

Demographic Variable	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=6	BGJ398 90mg + BYL719 300mg N=5	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=31	All patients N=62
Age (Years)								
n	4	4	6	6	5	6	31	62
Mean	56.0	49.8	62.8	63.0	65.4	63.2	56.1	58.4
SD	10.42	11.59	8.66	7.13	3.29	11.58	10.81	10.47
Median	57.5	50.5	64.0	61.5	66.0	64.5	57.0	60.0
Minimum	42	37	51	56	60	42	30	30
Maximum	67	61	72	75	68	74	78	78
Age category (Years)-n(%)								
18 - <65	3 (75.0)	4 (100)	3 (50.0)	4 (66.7)	1 (20.0)	3 (50.0)	25 (80.6)	43 (69.4)
65 - <85	1 (25.0)	0	3 (50.0)	2 (33.3)	4 (80.0)	3 (50.0)	6 (19.4)	19 (30.6)
>= 85	0	0	0	0	0	0	0	0
Sex-n(%)								
Female	4 (100)	3 (75.0)	3 (50.0)	5 (83.3)	2 (40.0)	5 (83.3)	17 (54.8)	39 (62.9)
Male	0	1 (25.0)	3 (50.0)	1 (16.7)	3 (60.0)	1 (16.7)	14 (45.2)	23 (37.1)
Race-n(%)								
Caucasian	3 (75.0)	3 (75.0)	6 (100)	5 (83.3)	3 (60.0)	6 (100)	25 (80.6)	51 (82.3)
Black	0	0	0	0	0	0	1 (3.2)	1 (1.6)
Asian	1 (25.0)	1 (25.0)	0	0	2 (40.0)	0	2 (6.5)	6 (9.7)
Unknown	0	0	0	1 (16.7)	0	0	3 (9.7)	4 (6.5)
Ethnicity-n(%)								
Hispanic/Latino	1 (25.0)	1 (25.0)	1 (16.7)	2 (33.3)	0	2 (33.3)	7 (22.6)	14 (22.6)
East Asian	0	0	0	0	0	0	2 (6.5)	2 (3.2)
South Asian	0	0	0	0	1 (20.0)	0	0	1 (1.6)
Southeast Asian	1 (25.0)	1 (25.0)	0	0	0	0	0	2 (3.2)
Not Reported	1 (25.0)	2 (50.0)	1 (16.7)	1 (16.7)	2 (40.0)	0	8 (25.8)	15 (24.2)
Other	1 (25.0)	0	4 (66.7)	3 (50.0)	0	3 (50.0)	13 (41.9)	24 (38.7)

Demographic Variable	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=6	BGJ398 90mg + BYL719 300mg N=5	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=31	All patients N=62
Unknown	0	0	0	0	2 (40.0)	1 (16.7)	1 (3.2)	4 (6.5)
Weight (Kg)								
n	4	4	6	6	5	6	30	61
Mean	63.90	57.98	68.77	77.07	67.70	67.83	77.68	72.76
SD	13.805	6.728	11.868	14.042	11.678	7.209	24.125	19.355
Median	62.10	58.10	65.85	82.40	67.60	66.75	72.00	69.00
Minimum	49.0	50.0	57.8	49.6	52.7	61.5	46.5	46.5
Maximum	82.4	65.7	86.5	86.5	79.9	81.0	169.0	169.0
Height (cm)								
n	4	4	6	6	4	6	30	60
Mean	164.15	157.50	166.33	165.67	167.10	168.60	168.48	166.88
SD	2.982	5.260	8.042	7.737	5.074	8.099	13.106	10.582
Median	163.50	159.00	167.00	167.50	167.60	168.80	167.50	165.25
Minimum	161.6	150.0	155.0	155.0	161.0	157.0	144.0	144.0
Maximum	168.0	162.0	177.0	173.0	172.2	180.0	194.0	194.0
ECOG performance status (WHO) [a]-n(%)								
0	1 (25.0)	2 (50.0)	1 (16.7)	3 (50.0)	2 (40.0)	0	18 (58.1)	27 (43.5)
1	3 (75.0)	2 (50.0)	5 (83.3)	3 (50.0)	3 (60.0)	6 (100)	13 (41.9)	35 (56.5)
PIK3CA								
Mutation	4 (100)	4 (100)	6 (100)	6 (100)	5 (100)	5 (83.3)	30 (96.8)	60 (96.8)
FGFR1 status								
Mutation	0	0	0	0	0	0	0	0
Translocation	0	0	0	0	0	0	0	0
Amplification	0	0	0	0	0	0	5 (16.1)	5 (8.1)
FGFR2 status								
Mutation	0	0	0	0	0	0	4 (12.9)	4 (6.5)
Translocation	0	0	0	0	0	0	0	0

Demographic Variable	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=6	BGJ398 90mg + BYL719 300mg N=5	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=31	All patients N=62
Amplification	0	0	0	0	0	0	1 (3.2)	1 (1.6)
FGFR3 status								
Mutation	0	0	0	0	0	0	1 (3.2)	1 (1.6)
Translocation	0	0	0	0	0	0	1 (3.2)	1 (1.6)
Amplification	0	0	0	0	0	0	1 (3.2)	1 (1.6)

- a 0 - Fully active, able to carry on all pre-disease performance without restriction; 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature,e.g., light house work, office work; 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.

Summary of Efficacy

Primary Outcome Result(s)

Posterior distribution of DLT rates at the time of the last dose-escalation meeting (Dose-determining set)

Treatment		Posterior probabilities (%) that Pr(DLT) is in interval:			Mean	SD	Quantile		
BGJ398(mg)	BYL719(mg)	[0-0.16)	[0.16-0.35)	[0.35-1]			2.5%	50%	97.5%
20	300	0.905	0.095	0.001	0.094	0.048	0.026	0.086	0.212
20	400	0.545	0.442	0.013	0.161	0.069	0.049	0.152	0.319
40	300	0.888	0.111	0.000	0.104	0.045	0.036	0.097	0.209
75	300	0.766	0.233	0.001	0.126	0.052	0.043	0.119	0.244
90	300	0.683	0.313	0.004	0.137	0.062	0.041	0.129	0.279
100	300	0.632	0.359	0.009	0.145	0.071	0.038	0.135	0.308
125	300	0.542	0.404	0.054	0.167	0.099	0.030	0.150	0.405

Dose limiting toxicities by primary system organ class and preferred term (Dose-determining set)

Primary system organ class Preferred terms	BGJ398 20mg + BYL719 300mg N=3 n (%)	BGJ398 20mg + BYL719 400mg N=2 n (%)	BGJ398 40mg + BYL719 300mg N=5 n (%)	BGJ398 75mg + BYL719 300mg N=5 n (%)	BGJ398 90mg + BYL719 300mg N=3 n (%)	BGJ398 100mg + BYL719 300mg N=4 n (%)	BGJ398 125mg + BYL719 300mg N=6 n (%)	All patients N=28 n (%)
Any primary system organ class								
-Total	0	0	1 (20.0)	1 (20.0)	0	1 (25.0)	0	3 (10.7)
GASTROINTESTINAL DISORDERS								
-Total	0	0	0	1 (20.0)	0	1 (25.0)	0	2 (7.1)
STOMATITIS	0	0	0	1 (20.0)	0	1 (25.0)	0	2 (7.1)
METABOLISM AND NUTRITION DISORDERS								
-Total	0	0	1 (20.0)	0	0	0	0	1 (3.6)
HYPERGLYCAEMIA	0	0	1 (20.0)	0	0	0	0	1 (3.6)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the "All patients".

- A patient with multiple occurrences of a DLT under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple DLTs within a primary system organ class is counted only once in the total row.

Secondary Outcome Result(s)

Summary of best overall response by treatment as per RECIST 1.1 (Full analysis set)

	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 [b] n (%)	All patients N=62 n (%)
Best overall response								
Complete response (CR)	0	0	0	0	0	0	0	0
Partial response (PR)	0	0	0	1 (16.7)	1 (20.0)	0	4 (12.9)	6 (9.7)
Non-CR/Non-PD (NCRNPD)[a]	0	0	0	0	0	0	2 (6.5)	2 (3.2)
Stable disease (SD)	2 (50.0)	3 (75.0)	3 (50.0)	2 (33.3)	3 (60.0)	0	15 (48.4)	28 (45.2)
Progressive disease (PD)	2 (50.0)	1 (25.0)	3 (50.0)	1 (16.7)	1 (20.0)	4 (66.7)	9 (29.0)	21 (33.9)
Unknown	0	0	0	2 (33.3)	0	2 (33.3)	1 (3.2)	5 (8.1)
Overall response rate (ORR) (CR or PR)	0	0	0	1 (16.7)	1 (20.0)	0	4 (12.9)	6 (9.7)
Disease control rate (DCR) (CR or PR or SD)	2 (50.0)	3 (75.0)	3 (50.0)	3 (50.0)	4 (80.0)	0	19 (61.3)	34 (54.8)

- Best overall response is based on Investigator's assessment of disease status using RECIST v1.1 criteria.
- N: The total number of patients in the treatment group. It is the denominator for percentage (%) calculation.
- n: Number of patients who are at the corresponding category.
- a Patients only have non-target lesions at Baseline.
- b One patient, treated at the RDE, was reported as having the PIK3CA mutation at the time of screening and therefore enrolled per protocol. The investigational site incorrectly changed the PIK3CA mutation status to "No" on the CRF page in Janurary 2017. Recorded as not having the PIK3CA mutation in the database, the patient could no longer be grouped into the Expansion Treatment Arm 2. As a result, this patient was excluded even though the patient was treated at the RDE.

Summary of best overall response by treatment as per RECIST 1.1 for patients treated at MTD/RDE (Full analysis set)

	Escalation BGJ398 125mg + BYL719 300mg N=7 n (%)	Expansion Treatment Arm 1 N=5 n (%)	Expansion Treatment Arm 2 N=12 n (%)	Expansion Treatment Arm 3 N=6 n (%)	All patients N=30 n (%)
Best overall response					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	0	0	2 (16.7)	2 (33.3)	4 (13.3)
Non-CR/Non-PD (NCRNPD)*	1 (14.3)	1 (20.0)	0	0	2 (6.7)
Stable disease (SD)	4 (57.1)	2 (40.0)	6 (50.0)	2 (33.3)	14 (46.7)
Progressive disease (PD)	2 (28.6)	1 (20.0)	4 (33.3)	2 (33.3)	9 (30.0)
Unknown	0	1 (20.0)	0	0	1 (3.3)
Overall response rate (ORR) (CR or PR)	0	0	2 (16.7)	2 (33.3)	4 (13.3)
Disease control rate (DCR) (CR or PR or SD)	4 (57.1)	2 (40.0)	8 (66.7)	4 (66.7)	18 (60.0)

- Best overall response is based on Investigator's assessment of disease status using RECIST v1.1 criteria.
- Treatment arms are defined as: Expansion Treatment Arm 1: breast cancer patients with PIK3CA mutation and FGFR alteration (amplification, mutation or translocation). Expansion Treatment Arm 2: patients, regardless of primary site of cancer, with PIK3CA mutation and no FGFR alteration. Two patients with breast cancer and no FGFR alteration were included in this arm. Expansion Treatment Arm 3: non-breast cancer patients with PIK3CA mutation and FGFR alteration.
- N: The total number of patients in the treatment arm. It is the denominator for percentage (%) calculation.
- n: Number of patients who are at the corresponding category.
- * Patients only have non-target lesions at Baseline.

Analysis of PFS per RECIST 1.1 using Kaplan-Meier method for patients treated at MTD/RDE (Full analysis set)

	Escalation BGJ398 125mg + BYL719 300mg N=7	Expansion Treatment Arm 1 N=5	Expansion Treatment Arm 2 N=12	Expansion Treatment Arm 3 N=6	All patients N=30
No. of PFS events					
Progression	4 (57.1%)	2 (40.0%)	10 (83.3%)	4 (66.7%)	20 (66.7%)
Death	0	1 (20.0%)	0	0	1 (3.3%)
No. of censored[a]	3 (42.9%)	2 (40.0%)	2 (16.7%)	2 (33.3%)	9 (30.0%)
Kaplan-Meier estimates (%) PFS rate [95% CI] at:					
2 months	N/A	N/A	65.63 [32.04, 85.57]	N/A	71.78 [51.35, 84.80]
4 months	N/A	N/A	37.50 [11.74, 63.82]	N/A	43.72 [23.38, 62.44]
6 months	N/A	N/A	12.50 [0.76, 41.23]	N/A	21.86 [7.18, 41.56]
12 months	N/A	N/A	NE	N/A	NE
Median PFS [95% CI]	3.71 [1.35, NE]	4.01 [2.10, 7.75]	3.68 [1.41, 5.49]	4.21 [1.08, 9.03]	3.71 [2.10,5.39]

- a These patients were censored based on “Adequate assessment no longer available” entry entered in the database.
- Treatment arms are defined as: Expansion Treatment Arm 1: breast cancer patients with PIK3CA mutation and FGFR alteration (amplification, mutation or translocation). Expansion Treatment Arm 2: patients, regardless of primary site of cancer, with PIK3CA mutation and no FGFR alteration. Two patients with breast cancer and no FGFR alteration were included in this arm. Expansion Treatment Arm 3: non-breast cancer patients with PIK3CA mutation and FGFR alteration.
- Kaplan-Meier estimates are provided for each group with at least 10 patients enrolled and treated at the MTD/RDE.
- NE: not estimable

Summary of pharmacokinetic parameters for BGJ398 by treatment - Profile Day: Cycle 1 Day 1 (Pharmacokinetic analysis set)

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
AUC(0-24hr) (hr*ng/mL)	n	4	4	4	5	3	4	25
	Mean (SD)	23.4 (13.4)	48.8 (26.8)	248 (253)	217 (227)	432 (260)	786 (702)	836 (770)
	CV%	57.5	54.9	102.2	104.6	60.2	89.3	92.1
	Geo-mean	20.9	38.5	111	147	374	507	516
	Geo-CV%	58.0	120.7	452.8	128.4	77.7	173.1	172.6
	Median	19.4	59.1	223	148	418	699	618
	[Min; Max]	[12.4; 42.3]	[9.33; 67.4]	[12.6; 533]	[38.8; 614]	[179; 698]	[130; 1610]	[15.2; 2960]
Cmax (ng/mL)	n	4	4	6	5	4	6	28
	Mean (SD)	5.75 (2.16)	10.5 (6.92)	40.1 (38.9)	40.6 (33)	71.3 (45.4)	59.2 (50.1)	128 (123)
	CV%	37.5	65.8	96.9	81.3	63.8	84.6	96.3
	Geo-mean	5.48	8.72	20.6	30	61.9	42.6	76.1
	Geo-CV%	35.8	85.9	256.7	117.6	66.0	116.7	180.8
	Median	5.1	9.44	30.3	34.4	58.1	43.9	81.8
	[Min; Max]	[4; 8.82]	[3.28; 19.9]	[3.24; 87.3]	[7.51; 94.4]	[32.9; 136]	[11.4; 145]	[2.52; 542]
Tmax (hr)	n	4	4	6	5	4	6	28
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Median	2.5	2.54	2.05	2.08	2.57	2.54	2.93
	[Min; Max]	[2; 3.03]	[1.92; 4.08]	[1.93; 3]	[2; 3.08]	[2; 8]	[2.02; 7.97]	[1; 23.9]
T1/2 (hr)	n	4	2	2	5	3	4	24
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
	Median	2.51	3.08	6.77	3.22	4.69	7.95	5.39
	[Min; Max]	[1.9; 3.1]	[2.75; 3.42]	[5.9; 7.65]	[1.7; 6.38]	[2.55; 5.22]	[3.86; 11.7]	[3; 9.59]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

Summary of pharmacokinetic parameters for BGJ398 by treatment - Profile Day: Cycle 1 Day 15 (Pharmacokinetic analysis set)

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
AUC(0-24hr) (hr*ng/mL)	n	4	2	4	4	4	3	19
	Mean (SD)	86 (83.7)	60.7 (53.2)	439 (687)	953 (1060)	2690 (1960)	1200 (960)	2890 (1870)
	CV%	97.4	87.6	156.4	111.0	73.0	80.1	64.6
	Geo-mean	64.6	47.6	144	617	2140	737	2210
	Geo-CV%	96.4	136.3	496.1	141.3	95.8	274.3	106.6
	Median	47.8	60.7	136	527	2360	1450	2250
	[Min; Max]	[37.4; 211]	[23.1; 98.3]	[20.9; 1460]	[254; 2500]	[941; 5110]	[137; 2010]	[224; 7110]
Cmax (ng/mL)	n	4	3	5	5	4	4	19
	Mean (SD)	13.7 (11.1)	9.2 (6.39)	77.9 (90)	104 (88.1)	202 (136)	89.4 (63.2)	218 (126)
	CV%	81.0	69.5	115.6	84.5	67.1	70.7	57.8
	Geo-mean	11.1	7.24	33.3	76.7	164	68	170
	Geo-CV%	83.2	117.6	363.9	108.8	89.8	119.2	102.9
	Median	9.76	9.74	28.6	57.5	203	90.3	229
	[Min; Max]	[5.3; 30.1]	[2.55; 15.3]	[4.45; 206]	[30; 231]	[79.9; 322]	[19.8; 157]	[17.4; 431]
Tmax (hr)	n	4	3	5	5	4	4	19
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Median	2.04	4	3	3	3.07	3.42	2.98
	[Min; Max]	[1.97; 3]	[3; 26.9]	[2.03; 4.25]	[2; 6]	[1; 3.83]	[2; 7]	[1.77; 4.33]
T1/2 (hr)	n	4	1	4	4	3	3	17
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Median	3.1	3.92	5.24	7.46	20.5	6.75	12.8
	[Min; Max]	[2.76; 6.95]	[3.92; 3.92]	[3.38; 11.2]	[6.4; 33.6]	[6.93; 20.8]	[5.66; 9.45]	[6.03; 77.5]
Racc	n	4	2	2	4	3	2	17
	Mean (SD)	3.41 (1.61)	2.02 (0.645)	4.16 (2.01)	7.62 (6.37)	7.48 (4.11)	3.18 (2.74)	27.5 (82.2)
	CV%	47.3	32.0	48.3	83.7	54.9	86.2	299.4
	Geo-mean	3.1	1.96	3.91	5.98	6.83	2.52	5.23
	Geo-CV%	55.8	33.4	53.6	92.7	53.8	131.3	296.9
	Median	3.49	2.02	4.16	5.5	5.26	3.18	3.79
	[Min; Max]	[1.68; 4.98]	[1.56; 2.47]	[2.74; 5.58]	[2.61; 16.9]	[4.97; 12.2]	[1.24; 5.12]	[0.394; 343]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

Summary of pharmacokinetic parameters for BGJ398 by treatment - Profile Day: Cycle 2 Day 1 (Pharmacokinetic analysis set)

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
AUC(0-24hr) (hr*ng/mL)	n	3	3	3	4	3	2	17
	Mean (SD)	58.5 (50.7)	48.9 (23.8)	550 (435)	328 (473)	1030 (551)	730 (815)	1050 (504)
	CV%	86.7	48.6	79.1	144.0	53.5	111.8	48.0
	Geo-mean	40.3	45.4	441	122	898	447	925
	Geo-CV%	172.0	48.6	98.0	452.7	78.6	299.3	58.9
	Median	52.2	39.6	410	135	1230	730	1020
	[Min; Max]	[11.2; 112]	[31.1; 75.9]	[202; 1040]	[16.8; 1030]	[405; 1450]	[153; 1310]	[301; 1890]
Cmax (ng/mL)	n	3	4	4	4	4	3	22
	Mean (SD)	12.7 (9.38)	9.06 (7.72)	43.8 (34.4)	37.5 (48.9)	93.5 (73.1)	111 (86)	116 (69.2)
	CV%	74.1	85.3	78.6	130.5	78.1	77.8	59.4
	Geo-mean	9.45	7.3	27.7	16.7	60.8	80	96.2
	Geo-CV%	142.3	79.8	226.2	344.6	200.3	156.3	74.7
	Median	13.5	5.46	43.3	19.2	99.8	114	99.9
	[Min; Max]	[2.89; 21.6]	[4.7; 20.6]	[4.06; 84.4]	[2.51; 109]	[10.5; 164]	[23; 195]	[20.6; 284]
Tmax (hr)	n	3	4	4	4	4	3	22
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Median	2.08	3.07	2	2.08	2.5	4.08	4.02
	[Min; Max]	[1.93; 3]	[2.08; 4]	[2; 2.05]	[2.08; 4]	[2; 3.78]	[4; 6]	[1.92; 23.5]
T1/2 (hr)	n	3	1	3	3	3	2	14
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Median	2.49	3.43	6.25	4.93	6.17	7.73	6.64
	[Min; Max]	[2.32; 3.1]	[3.43; 3.43]	[5.24; 8.59]	[2.5; 8.74]	[4.65; 10]	[5.89; 9.58]	[2.16; 10.4]
Racc	n	3	3	2	4	3	1	16
	Mean (SD)	2.44 (1.87)	2.01 (1.97)	1.72 (1.34)	1.06 (0.496)	2.73 (1.27)	10.1 (N/A)	4.02 (8.31)
	CV%	76.5	98.2	78.2	46.8	46.3	N/A	206.7
	Geo-mean	1.75	1.42	1.43	0.97	2.55	10.1	1.98
	Geo-CV%	163.3	135.4	108.3	52.8	46.4	N/A	124.4
	Median	2.65	1.21	1.72	1.02	2.26	10.1	1.59
	[Min; Max]	[0.483; 4.2]	[0.563; 4.25]	[0.768; 2.67]	[0.534; 1.67]	[1.77; 4.16]	[10.1; 10.1]	[0.744; 34.8]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

Summary of pharmacokinetic parameters of BYL719 by treatment - Profile Day: Cycle 1 Day 1 (Pharmacokinetic analysis set)

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
AUC(0-24hr) (hr*ng/mL)	n	4	4	6	5	3	6	26
	Mean (SD)	22400 (1820)	31600 (20800)	17900 (6810)	18200 (9820)	12700 (7450)	19300 (7580)	18500 (7810)
	CV%	8.1	65.8	38.0	53.9	58.5	39.2	42.2
	Geo-mean	22400	25500	16600	16300	11300	18100	16800
	Geo-CV%	7.9	96.3	48.9	58.1	68.5	41.3	50.7
	Median	21700	31800	19700	17100	11500	18200	17400
	[Min; Max]	[21200; 25100]	[9200; 53900]	[7400; 26500]	[7960; 33800]	[6000; 20700]	[10200; 31600]	[3970; 35400]
Cmax (ng/mL)	n	4	4	6	5	4	6	28
	Mean (SD)	2320 (914)	2770 (1480)	2100 (838)	1600 (806)	1440 (798)	1840 (1000)	1880 (948)
	CV%	39.4	53.5	39.9	50.5	55.3	54.6	50.4
	Geo-mean	2200	2450	1900	1440	1280	1600	1670
	Geo-CV%	39.7	65.4	59.8	54.8	61.4	65.5	55.7
	Median	2140	2890	2250	1580	1300	1650	1780
	[Min; Max]	[1460; 3560]	[1250; 4070]	[662; 2850]	[728; 2850]	[655; 2520]	[695; 3080]	[549; 5100]
Tmax (hr)	n	4	4	6	5	4	6	28
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Median	3.08	2.5	2.08	2	1.61	2.98	2.08
	[Min; Max]	[1.08; 6]	[1; 6]	[1; 3.47]	[1; 2.08]	[1; 6]	[1.08; 3.08]	[0.933; 6.17]
T1/2 (hr)	n	3	3	6	5	3	6	26
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Median	7.73	5.72	8.76	7.46	6.38	7.05	7.45
	[Min; Max]	[7.58; 9.32]	[5.12; 6.6]	[6.6; 17.4]	[6.76; 16.7]	[6.29; 6.51]	[5.05; 21.7]	[4.56; 14.4]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

Summary of pharmacokinetic parameters of BYL719 by treatment - Profile Day: Cycle 1 Day 15 (Pharmacokinetic analysis set)

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
AUC(0-24hr) (hr*ng/mL)	n	4	2	3	4	4	2	18
	Mean (SD)	34400 (10700)	16800 (3520)	21600 (7180)	19300 (5840)	23800 (8320)	25200 (12100)	25900 (9800)
	CV%	31.0	21.0	33.2	30.3	35.0	48.1	37.9
	Geo-mean	33100	16600	20800	18700	22400	23700	24200
	Geo-CV%	34.8	21.4	36.5	29.9	44.7	53.4	39.3
	Median	35000	16800	22100	17900	26300	25200	24100
	[Min; Max]	[20900; 46800]	[14300; 19200]	[14200; 28500]	[14400; 27000]	[12100; 30600]	[16600; 33800]	[11300; 47800]
Cmax (ng/mL)	n	4	2	4	5	4	4	19
	Mean (SD)	2940 (1130)	1320 (551)	2350 (830)	1790 (686)	2100 (533)	1490 (666)	2130 (786)
	CV%	38.4	41.7	35.3	38.3	25.4	44.7	36.9
	Geo-mean	2720	1260	2210	1690	2060	1390	1960
	Geo-CV%	52.0	45.1	46.0	38.1	24.4	43.2	46.2
	Median	3310	1320	2580	1630	1960	1280	2080
	[Min; Max]	[1330; 3810]	[931; 1710]	[1160; 3080]	[1110; 2850]	[1640; 2850]	[986; 2430]	[767; 3410]
Tmax (hr)	n	4	2	4	5	4	4	19
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Median	2.5	3.79	1.08	4	3.46	3.87	3
	[Min; Max]	[1.97; 3]	[3; 4.58]	[1; 4.25]	[2; 6]	[1; 24.5]	[1.97; 6]	[0.967; 6.28]
T1/2 (hr)	n	4	1	3	3	3	2	18
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Median	7.82	6.71	9.86	8.31	6.96	8.42	8.24
	[Min; Max]	[7.35; 14.4]	[6.71; 6.71]	[7.88; 17.5]	[8.21; 10.5]	[6.23; 12.7]	[5.69; 11.2]	[5.12; 27]
Racc	n	4	2	3	4	3	2	15
	Mean (SD)	1.61 (0.479)	1.27 (0.397)	1.3 (0.567)	1.75 (1.13)	1.86 (0.33)	0.961 (0.152)	1.47 (0.625)
	CV%	29.8	31.3	43.6	64.7	17.8	15.8	42.6
	Geo-mean	1.55	1.24	1.2	1.52	1.84	0.96	1.36
	Geo-CV%	34.0	32.6	56.1	64.4	19.1	15.9	41.9
	Median	1.66	1.27	1.5	1.38	2.01	0.961	1.33
	[Min; Max]	[0.974; 2.13]	[0.989; 1.55]	[0.659; 1.74]	[0.842; 3.39]	[1.48; 2.08]	[0.854; 1.07]	[0.667; 3.26]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

Summary of pharmacokinetic parameters of BYL719 by treatment - Profile Day: Cycle 2 Day 1 (Pharmacokinetic analysis set)

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
AUC(0-24hr) (hr*ng/mL)	n	3	4	5	4	4	3	20
	Mean (SD)	33300 (10500)	30800 (14100)	22300 (16000)	23700 (12000)	25000 (2070)	28600 (8440)	25200 (9370)
	CV%	31.6	45.8	71.7	50.7	8.3	29.6	37.1
	Geo-mean	32100	27900	18000	21900	24900	27800	23600
	Geo-CV%	35.3	59.6	85.7	45.3	8.4	28.3	40.8
	Median	35300	31700	19900	18300	25100	24000	26400
	[Min; Max]	[22000; 42800]	[12900; 47100]	[7700; 47300]	[16600; 41700]	[22400; 27400]	[23300; 38300]	[10300; 49100]
Cmax (ng/mL)	n	3	4	5	4	4	3	22
	Mean (SD)	3600 (1830)	2240 (694)	1770 (898)	1730 (948)	2240 (614)	2340 (396)	2320 (841)
	CV%	50.7	31.0	50.6	54.9	27.4	16.9	36.3
	Geo-mean	3200	2140	1580	1580	2160	2320	2150
	Geo-CV%	72.1	36.1	59.2	49.4	33.5	17.1	43.2
	Median	4350	2330	1580	1320	2490	2320	2390
	[Min; Max]	[1520; 4940]	[1310; 2980]	[731; 3040]	[1140; 3140]	[1330; 2660]	[1960; 2750]	[787; 3780]
Tmax (hr)	n	3	4	5	4	4	3	22
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Median	3	4.04	2	3.55	2.38	4	2.99
	[Min; Max]	[1.93; 3.33]	[2.08; 4.13]	[1.08; 6]	[2.08; 4.15]	[2; 4]	[3; 4.08]	[0.983; 6.08]
T1/2 (hr)	n	3	3	3	4	4	3	18
	Mean (SD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Parameter	Statistics	BGJ398 20mg + BYL719 300mg N=4	BGJ398 20mg + BYL719 400mg N=4	BGJ398 40mg + BYL719 300mg N=6	BGJ398 75mg + BYL719 300mg N=5	BGJ398 90mg + BYL719 300mg N=4	BGJ398 100mg + BYL719 300mg N=6	BGJ398 125mg + BYL719 300mg N=29
	Geo-CV%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Median	8.82	7.36	7.71	8.9	5.79	7.6	6.84
	[Min; Max]	[6.37; 12.6]	[6.18; 9.28]	[6.17; 13.8]	[6.2; 20.9]	[4.94; 18.7]	[6.76; 8.24]	[4.52; 11.1]
Racc	n	3	4	5	4	3	3	20
	Mean (SD)	1.46 (0.462)	1.88 (2.16)	1.28 (0.404)	1.55 (0.449)	2.57 (1.51)	1.87 (0.792)	1.53 (0.49)
	CV%	31.7	115.2	31.5	28.9	58.7	42.4	32.0
	Geo-mean	1.41	1.26	1.23	1.51	2.29	1.77	1.46
	Geo-CV%	32.8	119.6	34.4	26.6	64.2	42.7	32.9
	Median	1.41	0.865	1.25	1.38	2.15	1.62	1.44
	[Min; Max]	[1.03; 1.95]	[0.662; 5.12]	[0.764; 1.78]	[1.24; 2.22]	[1.32; 4.25]	[1.23; 2.76]	[0.752; 2.64]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = sd/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

Summary of Safety

Safety Results

All adverse events, regardless of study treatment relationship, by primary system organ class and treatment (Safety set)

Primary system organ class	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
-Total	4 (100)	4 (100)	6 (100)	6 (100)	5 (100)	6 (100)	31(100)	62(100)
GASTROINTESTINAL DISORDERS	3 (75.0)	3 (75.0)	5 (83.3)	6 (100)	4 (80.0)	6 (100)	30(96.8)	57(91.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (75.0)	3 (75.0)	5 (83.3)	6 (100)	5 (100)	5 (83.3)	27(87.1)	54(87.1)
METABOLISM AND NUTRITION DISORDERS	3 (75.0)	3 (75.0)	4 (66.7)	5 (83.3)	4 (80.0)	5 (83.3)	29(93.5)	53(85.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (75.0)	3 (75.0)	3 (50.0)	3 (50.0)	4 (80.0)	2 (33.3)	23(74.2)	41(66.1)
INVESTIGATIONS	3 (75.0)	2 (50.0)	3 (50.0)	2 (33.3)	3 (60.0)	5 (83.3)	21(67.7)	39(62.9)
NERVOUS SYSTEM DISORDERS	2 (50.0)	2 (50.0)	3 (50.0)	2 (33.3)	4 (80.0)	3 (50.0)	16(51.6)	32(51.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (75.0)	1 (25.0)	3 (50.0)	2 (33.3)	2 (40.0)	4 (66.7)	14(45.2)	29(46.8)
INFECTIONS AND INFESTATIONS	3 (75.0)	2 (50.0)	3 (50.0)	3 (50.0)	2 (40.0)	3 (50.0)	7 (22.6)	23(37.1)
EYE DISORDERS	0	0	0	1 (16.7)	2 (40.0)	2 (33.3)	17(54.8)	22(35.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (50.0)	1 (25.0)	1 (16.7)	2 (33.3)	2 (40.0)	2 (33.3)	10(32.3)	20(32.3)
RENAL AND URINARY DISORDERS	1 (25.0)	1 (25.0)	2 (33.3)	1 (16.7)	1 (20.0)	0	8 (25.8)	14(22.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	1 (25.0)	1 (16.7)	1 (16.7)	2 (40.0)	2 (33.3)	6 (19.4)	13(21.0)
PSYCHIATRIC DISORDERS	2 (50.0)	0	1 (16.7)	1 (16.7)	2 (40.0)	2 (33.3)	5 (16.1)	13(21.0)
VASCULAR DISORDERS	2 (50.0)	0	1 (16.7)	1 (16.7)	1 (20.0)	2 (33.3)	4 (12.9)	11(17.7)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	0	0	0	5 (16.1)	5 (8.1)
EAR AND LABYRINTH DISORDERS	0	0	0	0	1 (20.0)	1 (16.7)	1 (3.2)	3 (4.8)

Primary system organ class	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1 (16.7)	1 (16.7)	0	0	1 (3.2)	3 (4.8)
CARDIAC DISORDERS	1 (25.0)	0	0	0	0	0	1 (3.2)	2 (3.2)
IMMUNE SYSTEM DISORDERS	0	0	0	0	0	0	2 (6.5)	2 (3.2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (25.0)	0	0	0	0	0	1 (3.2)	2 (3.2)
Not yet coded [a]	0	0	0	0	1 (20.0)	0	1 (3.2)	2 (3.2)

- a Two AEs were recorded in the database with “yes” to the question “Were any adverse events reported” and “General” as the category of the AE. However, no additional descriptive information was provided.
- Primary system organ classes are sorted in descending frequency, as reported in the “All patients” column.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
- Only AEs occurring during treatment or within 30 days of the last study medication are reported.

All and grade 3/4 adverse events, regardless of study treatment relationship, by preferred term and treatment (with at least a 10% incidence – all patients) (Safety set)

Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
-Total								
All grades	4 (100)	4 (100)	6 (100)	6 (100)	5 (100)	6 (100)	31 (100)	62 (100)
Grade 3/4	2 (50.0)	3 (75.0)	4 (66.7)	6 (100)	4 (80.0)	4 (66.7)	26 (83.9)	49 (79.0)
DIARRHOEA								
All grades	3 (75.0)	2 (50.0)	5 (83.3)	5 (83.3)	2 (40.0)	3 (50.0)	19 (61.3)	39 (62.9)
Grade 3/4	0	0	0	3 (50.0)	0	0	3 (9.7)	6 (9.7)
FATIGUE								
All grades	3 (75.0)	3 (75.0)	4 (66.7)	3 (50.0)	4 (80.0)	3 (50.0)	14 (45.2)	34 (54.8)
Grade 3/4	0	0	0	0	1 (20.0)	0	2 (6.5)	3 (4.8)
NAUSEA								
All grades	3 (75.0)	1 (25.0)	4 (66.7)	4 (66.7)	1 (20.0)	3 (50.0)	15 (48.4)	31 (50.0)
Grade 3/4	0	0	1 (16.7)	0	0	0	2 (6.5)	3 (4.8)
DECREASED APPETITE								
All grades	2 (50.0)	1 (25.0)	2 (33.3)	1 (16.7)	3 (60.0)	3 (50.0)	16 (51.6)	28 (45.2)
Grade 3/4	0	0	0	0	0	0	0	0
STOMATITIS								
All grades	1 (25.0)	2 (50.0)	2 (33.3)	3 (50.0)	3 (60.0)	2 (33.3)	15 (48.4)	28 (45.2)
Grade 3/4	0	0	0	1 (16.7)	0	1 (16.7)	6 (19.4)	8 (12.9)
HYPERGLYCAEMIA								
All grades	1 (25.0)	2 (50.0)	4 (66.7)	4 (66.7)	2 (40.0)	2 (33.3)	9 (29.0)	24 (38.7)
Grade 3/4	0	2 (50.0)	1 (16.7)	1 (16.7)	2 (40.0)	2 (33.3)	3 (9.7)	11 (17.7)
HYPERPHOSPHATAEMIA								
All grades	0	0	0	2 (33.3)	2 (40.0)	3 (50.0)	17 (54.8)	24 (38.7)
Grade 3/4	0	0	0	0	0	0	0	0
VOMITING								
All grades	1 (25.0)	1 (25.0)	2 (33.3)	1 (16.7)	0	3 (50.0)	13 (41.9)	21 (33.9)

Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
Grade 3/4	0	0	0	0	0	0	1 (3.2)	1 (1.6)
BLOOD CREATININE INCREASED								
All grades	0	0	1 (16.7)	1 (16.7)	2 (40.0)	4 (66.7)	10 (32.3)	18 (29.0)
Grade 3/4	0	0	0	0	0	1 (16.7)	0	1 (1.6)
DRY MOUTH								
All grades	1 (25.0)	1 (25.0)	1 (16.7)	3 (50.0)	0	1 (16.7)	11 (35.5)	18 (29.0)
Grade 3/4	0	0	0	0	0	0	0	0
DYSGEUSIA								
All grades	0	0	1 (16.7)	1 (16.7)	2 (40.0)	2 (33.3)	11 (35.5)	17 (27.4)
Grade 3/4	0	0	0	0	0	0	0	0
CONSTIPATION								
All grades	1 (25.0)	2 (50.0)	0	1 (16.7)	1 (20.0)	3 (50.0)	8 (25.8)	16 (25.8)
Grade 3/4	0	0	0	1 (16.7)	0	1 (16.7)	1 (3.2)	3 (4.8)
MUCOSAL INFLAMMATION								
All grades	0	0	1 (16.7)	0	3 (60.0)	1 (16.7)	10 (32.3)	15 (24.2)
Grade 3/4	0	0	0	0	0	1 (16.7)	2 (6.5)	3 (4.8)
ALANINE AMINOTRANSFERASE INCREASED								
All grades	0	0	0	0	1 (20.0)	1 (16.7)	10 (32.3)	12 (19.4)
Grade 3/4	0	0	0	0	0	0	6 (19.4)	6 (9.7)
ALOPECIA								
All grades	0	0	1 (16.7)	1 (16.7)	2 (40.0)	0	8 (25.8)	12 (19.4)
Grade 3/4	0	0	0	0	0	0	0	0
WEIGHT DECREASED								
All grades	1 (25.0)	0	0	2 (33.3)	2 (40.0)	2 (33.3)	5 (16.1)	12 (19.4)
Grade 3/4	0	0	0	0	0	0	0	0
ANAEMIA								
All grades	0	1 (25.0)	1 (16.7)	1 (16.7)	1 (20.0)	2 (33.3)	5 (16.1)	11 (17.7)

Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
Grade 3/4	0	1 (25.0)	1 (16.7)	0	0	0	1 (3.2)	3 (4.8)
ASPARTATE AMINOTRANSFERASE INCREASED								
All grades	0	1 (25.0)	0	0	1 (20.0)	1 (16.7)	8 (25.8)	11 (17.7)
Grade 3/4	0	0	0	0	0	0	1 (3.2)	1 (1.6)
ASTHENIA								
All grades	1 (25.0)	0	1 (16.7)	1 (16.7)	0	1 (16.7)	7 (22.6)	11 (17.7)
Grade 3/4	0	0	0	0	0	1 (16.7)	4 (12.9)	5 (8.1)
COUGH								
All grades	0	0	3 (50.0)	1 (16.7)	1 (20.0)	2 (33.3)	3 (9.7)	10 (16.1)
Grade 3/4	0	0	0	0	0	0	0	0
DRY SKIN								
All grades	0	0	1 (16.7)	1 (16.7)	1 (20.0)	1 (16.7)	6 (19.4)	10 (16.1)
Grade 3/4	0	0	0	0	0	0	0	0
PYREXIA								
All grades	2 (50.0)	1 (25.0)	1 (16.7)	0	1 (20.0)	0	5 (16.1)	10 (16.1)
Grade 3/4	0	0	0	0	0	0	1 (3.2)	1 (1.6)
RASH								
All grades	0	2 (50.0)	0	0	2 (40.0)	1 (16.7)	5 (16.1)	10 (16.1)
Grade 3/4	0	0	0	0	1 (20.0)	0	1 (3.2)	2 (3.2)
DYSPNOEA								
All grades	2 (50.0)	1 (25.0)	0	0	1 (20.0)	0	5 (16.1)	9 (14.5)
Grade 3/4	0	0	0	0	0	0	1 (3.2)	1 (1.6)
ABDOMINAL PAIN								
All grades	0	0	1 (16.7)	1 (16.7)	1 (20.0)	0	5 (16.1)	8 (12.9)
Grade 3/4	0	0	0	1 (16.7)	0	0	1 (3.2)	2 (3.2)
DRY EYE								
All grades	0	0	0	0	1 (20.0)	0	7 (22.6)	8 (12.9)

Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
Grade 3/4	0	0	0	0	0	0	1 (3.2)	1 (1.6)
GAMMA-GLUTAMYLTRANSFERASE INCREASED								
All grades	1 (25.0)	0	0	0	0	1 (16.7)	6 (19.4)	8 (12.9)
Grade 3/4	0	0	0	0	0	1 (16.7)	2 (6.5)	3 (4.8)
HYPOKALAEMIA								
All grades	2 (50.0)	0	0	1 (16.7)	2 (40.0)	0	3 (9.7)	8 (12.9)
Grade 3/4	0	0	0	0	0	0	0	0
INSOMNIA								
All grades	1 (25.0)	0	0	1 (16.7)	2 (40.0)	1 (16.7)	3 (9.7)	8 (12.9)
Grade 3/4	0	0	0	0	0	0	0	0
OEDEMA PERIPHERAL								
All grades	1 (25.0)	0	0	1 (16.7)	0	3 (50.0)	3 (9.7)	8 (12.9)
Grade 3/4	0	0	0	0	0	1 (16.7)	0	1 (1.6)
RASH MACULO-PAPULAR								
All grades	1 (25.0)	1 (25.0)	1 (16.7)	0	1 (20.0)	0	4 (12.9)	8 (12.9)
Grade 3/4	0	1 (25.0)	0	0	0	0	2 (6.5)	3 (4.8)
HYPOPHOSPHATAEMIA								
All grades	0	0	1 (16.7)	0	2 (40.0)	0	4 (12.9)	7 (11.3)
Grade 3/4	0	0	0	0	0	0	1 (3.2)	1 (1.6)
LIPASE INCREASED								
All grades	0	0	2 (33.3)	0	1 (20.0)	0	4 (12.9)	7 (11.3)
Grade 3/4	0	0	0	0	0	0	2 (6.5)	2 (3.2)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME								
All grades	0	0	0	0	1 (20.0)	0	6 (19.4)	7 (11.3)
Grade 3/4	0	0	0	0	1 (20.0)	0	1 (3.2)	2 (3.2)
URINARY TRACT INFECTION								

Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
All grades	1 (25.0)	0	0	2 (33.3)	1 (20.0)	1 (16.7)	2 (6.5)	7 (11.3)
Grade 3/4	0	0	0	1 (16.7)	0	0	0	1 (1.6)

- Preferred terms are sorted in descending frequency, as reported in the 'All patients' column and the 'All grades' row.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events is only counted under the total row.
- Only AEs occurring during treatment or within 30 days of the last study medication are reported.

Deaths, SAEs and other significant AEs by treatment (Safety set)

Category	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
All deaths	1 (25.0)	1 (25.0)	3 (50.0)	1 (16.7)	0	1 (16.7)	6 (19.4)	13 (21.0)
On-treatment deaths[a]	0	0	0	0	0	1 (16.7)	2 (6.5)	3 (4.8)
Adverse events	4 (100)	4 (100)	6 (100)	6 (100)	5 (100)	6 (100)	31 (100)	62 (100)
Suspected to be drug-related	3 (75.0)	4 (100)	6 (100)	6 (100)	5 (100)	6 (100)	31 (100)	61 (98.4)
Serious adverse events	4 (100)	2 (50.0)	3 (50.0)	4 (66.7)	0	3 (50.0)	11 (35.5)	27 (43.5)
Suspected to be drug-related	0	1 (25.0)	1 (16.7)	1 (16.7)	0	0	5 (16.1)	8 (12.9)
AEs leading to discontinuation	0	0	0	1 (16.7)	1 (20.0)	1 (16.7)	5 (16.1)	8 (12.9)
Suspected to be drug-related	0	0	0	1 (16.7)	1 (20.0)	1 (16.7)	5 (16.1)	8 (12.9)
AEs requiring dose interruption or reduction	3 (75.0)	2 (50.0)	4 (66.7)	5 (83.3)	4 (80.0)	4 (66.7)	26 (83.9)	48 (77.4)
Suspected to be drug-related	2 (50.0)	2 (50.0)	3 (50.0)	3 (50.0)	3 (60.0)	4 (66.7)	23 (74.2)	40 (64.5)
AEs requiring additional therapy	4 (100)	4 (100)	6 (100)	6 (100)	5 (100)	6 (100)	31 (100)	62 (100)
Suspected to be drug-related	3 (75.0)	3 (75.0)	6 (100)	6 (100)	5 (100)	6 (100)	30 (96.8)	59 (95.2)

- a On-treatment deaths: deaths up to 30 days after the last dose.

On-treatment deaths by preferred term and treatment (Safety set)

Primary cause of death Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
-Total	0	0	0	0	0	1 (16.7)	2 (6.5)	3 (4.8)
DISEASE PROGRESSION	0	0	0	0	0	1 (16.7)	2 (6.5)	3 (4.8)

- Preferred terms are sorted in descending frequency, as reported in the “All patients” column.
- On-treatment deaths: deaths up to 30 days after the last dose.

Serious adverse events, regardless of study treatment relationship, by primary system organ class, preferred term and treatment (Safety set)

Primary system organ class Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
Any primary system organ class								
-Total	4 (100)	2 (50.0)	3 (50.0)	4 (66.7)	0	3 (50.0)	11 (35.5)	27 (43.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS								
-Total	0	1 (25.0)	0	0	0	0	0	1 (1.6)
ANAEMIA	0	1 (25.0)	0	0	0	0	0	1 (1.6)
GASTROINTESTINAL DISORDERS								
-Total	0	0	1 (16.7)	3 (50.0)	0	0	4 (12.9)	8 (12.9)
DIARRHOEA	0	0	0	1 (16.7)	0	0	1 (3.2)	2 (3.2)
STOMATITIS	0	0	0	1 (16.7)	0	0	1 (3.2)	2 (3.2)
ABDOMINAL PAIN LOWER	0	0	0	1 (16.7)	0	0	0	1 (1.6)
CONSTIPATION	0	0	0	1 (16.7)	0	0	0	1 (1.6)
DYSPHAGIA	0	0	0	0	0	0	1 (3.2)	1 (1.6)
NAUSEA	0	0	1 (16.7)	0	0	0	0	1 (1.6)

Primary system organ class Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
RECTAL HAEMORRHAGE	0	0	0	1 (16.7)	0	0	0	1 (1.6)
SMALL INTESTINAL OBSTRUCTION	0	0	0	0	0	0	1 (3.2)	1 (1.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
-Total	2 (50.0)	0	1 (16.7)	1 (16.7)	0	1 (16.7)	3 (9.7)	8 (12.9)
PYREXIA	2 (50.0)	0	1 (16.7)	0	0	0	1 (3.2)	4 (6.5)
GENERAL PHYSICAL HEALTH DETERIORATION	0	0	0	0	0	0	2 (6.5)	2 (3.2)
OEDEMA PERIPHERAL	0	0	0	0	0	1 (16.7)	0	1 (1.6)
PERIPHERAL SWELLING	0	0	0	1 (16.7)	0	0	0	1 (1.6)
IMMUNE SYSTEM DISORDERS								
-Total	0	0	0	0	0	0	1 (3.2)	1 (1.6)
HYPERSENSITIVITY	0	0	0	0	0	0	1 (3.2)	1 (1.6)
INFECTIONS AND INFESTATIONS								
-Total	1 (25.0)	0	1 (16.7)	0	0	1 (16.7)	0	3 (4.8)
CLOSTRIDIUM DIFFICILE COLITIS	0	0	1 (16.7)	0	0	0	0	1 (1.6)
SEPTIC SHOCK	0	0	0	0	0	1 (16.7)	0	1 (1.6)
SKIN INFECTION	1 (25.0)	0	0	0	0	0	0	1 (1.6)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS								
-Total	0	0	0	1 (16.7)	0	0	1 (3.2)	2 (3.2)
FRACTURE	0	0	0	1 (16.7)	0	0	0	1 (1.6)
WOUND DECOMPOSITION	0	0	0	0	0	0	1 (3.2)	1 (1.6)
METABOLISM AND NUTRITION DISORDERS								
-Total	0	0	0	0	0	0	2 (6.5)	2 (3.2)
HYPERGLYCAEMIA	0	0	0	0	0	0	1 (3.2)	1 (1.6)
HYPONATRAEMIA	0	0	0	0	0	0	1 (3.2)	1 (1.6)

Primary system organ class Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS								
-Total	2 (50.0)	0	0	0	0	0	1 (3.2)	3 (4.8)
BACK PAIN	1 (25.0)	0	0	0	0	0	0	1 (1.6)
MUSCULAR WEAKNESS	1 (25.0)	0	0	0	0	0	0	1 (1.6)
PAIN IN EXTREMITY	0	0	0	0	0	0	1 (3.2)	1 (1.6)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)								
-Total	0	0	0	0	0	0	1 (3.2)	1 (1.6)
TUMOUR PAIN	0	0	0	0	0	0	1 (3.2)	1 (1.6)
NERVOUS SYSTEM DISORDERS								
-Total	1 (25.0)	0	1 (16.7)	0	0	0	0	2 (3.2)
HEADACHE	0	0	1 (16.7)	0	0	0	0	1 (1.6)
PERONEAL NERVE PALSY	1 (25.0)	0	0	0	0	0	0	1 (1.6)
PSYCHIATRIC DISORDERS								
-Total	0	0	1 (16.7)	0	0	0	0	1 (1.6)
DISORIENTATION	0	0	1 (16.7)	0	0	0	0	1 (1.6)
RENAL AND URINARY DISORDERS								
-Total	0	1 (25.0)	0	0	0	0	0	1 (1.6)
RENAL FAILURE	0	1 (25.0)	0	0	0	0	0	1 (1.6)
URETERIC OBSTRUCTION	0	1 (25.0)	0	0	0	0	0	1 (1.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS								
-Total	1 (25.0)	0	0	0	0	0	2 (6.5)	3 (4.8)
PLEURAL EFFUSION	1 (25.0)	0	0	0	0	0	1 (3.2)	2 (3.2)
DYSPNOEA	0	0	0	0	0	0	1 (3.2)	1 (1.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS								

Primary system organ class Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
-Total	0	1 (25.0)	0	0	0	0	0	1 (1.6)
RASH MACULO-PAPULAR	0	1 (25.0)	0	0	0	0	0	1 (1.6)
VASCULAR DISORDERS								
-Total	0	0	0	1 (16.7)	0	1 (16.7)	0	2 (3.2)
DEEP VEIN THROMBOSIS	0	0	0	1 (16.7)	0	1 (16.7)	0	2 (3.2)
HAEMATOMA	0	0	0	1 (16.7)	0	0	0	1 (1.6)
ILIAC VEIN OCCLUSION	0	0	0	1 (16.7)	0	0	0	1 (1.6)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the 'All patients' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
- Only AEs occurring during treatment or within 30 days of the last study medication are reported.

Adverse events leading to study drug discontinuation, regardless of study treatment relationship, by primary system organ class, preferred term and treatment (Safety set)

Primary system organ class Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
Any primary system organ class								
-Total	0	0	0	1 (16.7)	1 (20.0)	1 (16.7)	5 (16.1)	8 (12.9)
GASTROINTESTINAL DISORDERS								
-Total	0	0	0	1 (16.7)	0	0	3 (9.7)	4 (6.5)
DIARRHOEA	0	0	0	1 (16.7)	0	0	1 (3.2)	2 (3.2)
NAUSEA	0	0	0	1 (16.7)	0	0	1 (3.2)	2 (3.2)
ASCITES	0	0	0	0	0	0	1 (3.2)	1 (1.6)
STOMATITIS	0	0	0	0	0	0	1 (3.2)	1 (1.6)

Primary system organ class Preferred term	BGJ398 20mg + BYL719 300mg N=4 n (%)	BGJ398 20mg + BYL719 400mg N=4 n (%)	BGJ398 40mg + BYL719 300mg N=6 n (%)	BGJ398 75mg + BYL719 300mg N=6 n (%)	BGJ398 90mg + BYL719 300mg N=5 n (%)	BGJ398 100mg + BYL719 300mg N=6 n (%)	BGJ398 125mg + BYL719 300mg N=31 n (%)	All patients N=62 n (%)
VOMITING	0	0	0	0	0	0	1 (3.2)	1 (1.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
-Total	0	0	0	0	0	1 (16.7)	0	1 (1.6)
MUCOSAL INFLAMMATION	0	0	0	0	0	1 (16.7)	0	1 (1.6)
IMMUNE SYSTEM DISORDERS								
-Total	0	0	0	0	0	0	1 (3.2)	1 (1.6)
HYPERSENSITIVITY	0	0	0	0	0	0	1 (3.2)	1 (1.6)
INVESTIGATIONS								
-Total	0	0	0	0	0	0	1 (3.2)	1 (1.6)
BLOOD CREATININE INCREASED	0	0	0	0	0	0	1 (3.2)	1 (1.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS								
-Total	0	0	0	0	1 (20.0)	0	0	1 (1.6)
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	0	0	0	0	1 (20.0)	0	0	1 (1.6)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the 'All patients' column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.
- Only AEs occurring during treatment or within 30 days of the last study medication are reported.

Other Relevant Findings

Not applicable.

Conclusion:

•The RDE of 125 mg BGJ398 in combination with 300 mg BYL719 was declared, based on the emerging safety information, including DLT, PK, and PD data and was guided by the BLRM with EWOC principle.

•Overall, for all patients across a wide range of tumor types, the ORR was 9.7% (all PRs), with a corresponding DCR of 54.8%. At the RDE, the ORR and DCR were higher at 12.9% and 61.3%, respectively.

•The median PFS for all patients treated at the RDE was 3.7 months (95% CI: 2.1, 5.4).

•In general, BGJ398 exposure increased over-proportionately with dose, in spite of short half-life, BGJ398 accumulates significantly with repeated dosing and there was no or negligible interaction between BGJ398 and BYL719.

•Overall, the BGJ398 and BYL719 combination, at all dose levels administered, demonstrated that AEs were mild, manageable (with dose interruption and/or reductions), and reversible.

Date of Clinical Trial Report

28 July 2017