**Abbreviated Title:** BGJ398 in TIO

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**Title:** BGJ398 for the Treatment of Tumor-Induced Osteomalacia

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**Investigational Agents:**

| | |
|---|---|
| Drug Name: | BGJ398 |
| IND Number: | 138317 |
| Sponsor: | NIDCR |
| Manufacturer: | QED Therapeutics (QED)<br>(previously held by Novartis) |

**Collaborators:** CRADA with QED Pharmaceuticals

**For Multi-institutional protocols: Not Applicable**

## PRÉCIS

### Background:

- Tumor-induced osteomalacia (TIO) is a rare disorder in which fibroblast growth factor (FGF23)-producing neoplasms cause renal phosphate wasting and skeletal disease.
- Recent studies have shown that chromosomal translocations causing a fibronectin-FGFR1 (FN1/FGFR1) fusion gene have been identified in 40-60% of these tumors.
- BGJ398 is an orally bio-available, selective and ATP competitive pan-fibroblast growth factor receptor (FGFR) kinase inhibitor which has demonstrated anti-tumor activity in preclinical, in vitro and in-vivo tumor models harboring FGFR genetic alterations.

### Objectives:

To induce complete metabolic response in subjects with tumor-induced osteomalacia (TIO) with BGJ-398 as demonstrated by normalization of FGF23 and phosphate homeostasis.

### Eligibility:

Patients may be eligible if they:

- Are adults 18-85 years with documented evidence of TIO due to a non-localized or unresectable tumor, or metastatic disease, or resectable tumor that cannot be easily removed.
- Are not taking any exclusionary medications or foods that may interfere with BGJ398.
- Are not pregnant or nursing and are willing to use contraception (at least two forms of contraception), if able to become pregnant.
- Have no significant ophthalmologic, gastrointestinal, renal, or hematologic disease.

### Design:

- Phase 2, open-label, non-randomized, single-arm, drug treatment trial.
- 10 subjects to be studied.
- Treatment duration 6 months with 3 months off drug follow-up and optional extension phase.
- Monthly NIH visits with additional labs obtained in between visits.
- Imaging performed in those with identifiable tumors.
- Analyses to include repeated measures ANOVA assessing changes in biochemical indices over time in response to BGJ398.

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**List of Abbreviations**

| | |
|---|---|
| AE | Adverse Event |
| ALT | Alanine aminotransferase |
| ANC | Absolute Neutrophil Count |
| ANOVA | Analysis of variance |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| BMD | Bone mineral density |
| CBC | Complete Blood Count |
| CRF | Case Report Form |
| CT | Computed Tomography |
| CYP | Cytochrome p450 isoenzyme |
| DCC | Data Coordinating Center |
| DNA | Deoxyribonucleic Acid |
| DSMC | Data and Safety Monitoring Committee |
| eCRF | Electronic Case Report Form |
| eGFR | Estimated Glomerular Filtration Rate |
| FDA | Food and Drug Administration |
| FDG-PET/CT | fluorodeoxyglucose-positron emission tomography/CT |
| FGF23 | Fibroblast Growth Factor-23 |
| FGFR1 | Fibroblast Growth Factor Receptor-1 |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ITT | Intent-to treat |
| MCV | Mean Corpuscular Volume |
| NIDCR | National Institute of Dental and Craniofacial Research |
| BGJ398 | Tyrosine kinase inhibitor-investigational drug. |
| NIH | National Institutes of Health |
| PRPL | Patient Recruitment and Public Liaison |
| QoL | Quality of Life |
| RDW | Red Cell Distribution Width |
| RSC | Radiation Safety Committee |

| | |
|---|---|
| SAE | Serious Adverse Event |
| TIO | Tumor Induced Osteomalacia |
| TmP/GFR | Tubular maximum reabsorption of phosphate/GFR |
| TRP | Tubular reabsorption of phosphate |
| UP | Unanticipated Problem |
| ULN | Upper Limit Normal |
| WBC | White Blood Cells |

# 1. INTRODUCTION

## 1.1 STUDY OBJECTIVES

### 1.1.1 Primary Objective:

- To induce complete metabolic response in subjects with tumor-induced osteomalacia (TIO) with BGJ398 as demonstrated by normalization of FGF23 and phosphate homeostasis.

### 1.1.2 Secondary Objective:

- To evaluate the effects of BGJ398 on:
    - mineral homeostasis
    - quality of life
    - muscle strength.
- To evaluate the effects of BGJ-398 on radiographic evidence of TIO.

**Table 1** summarizes the primary, secondary and exploratory objectives tagged with the associated endpoints and evaluation criteria:

| | **Objective** | **Endpoint Measures** |
|---|---|---|
| **Primary** | Complete metabolic response | Normalization of blood phosphate and FGF23 off study drug |
| **Secondary/Exploratory** | Pharmacodynamics of mineral homeostasis response to BGJ398 in TIO | Changes in FGF23 (intact and C-terminal), Phosphorous, 1, 25 $(OH)_2$ vitamin D; TRP, TmP/GFR |
| | Effects on quality of life | Standardized measures of QoL |
| | Effects on muscle strength | Standardized muscle strength testing |
| | Effect on radiographic evidence of TIO | Changes in clinically-indicated FDG-PET/CT, octreotide SPECT/CT, or $^{68}$Ga-DOTATATE PET/CT scan |
| | Assess safety/tolerability | Percentage of patients who incurred grade 3 or 4 adverse events (AEs) or serious adverse events (SAE) or AEs causing dose interruption/reduction |

## 1.2 BACKGROUND AND RATIONALE

Tumor-induced osteomalacia (TIO) is a rare neoplastic syndrome that is associated with fractures, bone pain, and muscle weakness (*1*). The vast majority of cases are caused by fibroblast growth

factor-23 (FGF23)-secreting mixed connective tissue mesenchymal tumors. FGF23 acts by binding to target cells via an FGF receptor (FGFR1), but signaling requires the co-receptor Klotho (2). Activation of FGFR1 leads to inhibition of sodium-phosphate co-transporters in the proximal tubule cells, resulting in decreased tubular phosphate reabsorption, increased renal phosphate excretion, and hypophosphatemia (3). In addition, FGF23 downregulates 1α-hydroxylase and up-regulates 24-hydroxylase, resulting in decreased production of the active form of vitamin D, 1, 25-dihydroxy vitamin D, further contributing to hypophosphatemia. While tumor resection can cure TIO, tumors are typically small (often < 2 cm) and notoriously difficult to locate. Medical treatment of patients whose tumors cannot be located, or are inoperable or widely metastatic, is difficult. It involves at least thrice daily phosphate, which is poorly tolerated due to diarrhea, and active vitamin D. Frequent monitoring with careful adjustment of medications is required to prevent untoward effects of medical therapy, including secondary/tertiary hyperparathyroidism hypercalcemia, hypercalciuria, nephrocalcinosis, and nephrolithiasis.

Recently, translocations resulting in a fibronectin-fibroblast growth factor receptor-1 (FN1/FGFR1) fusion gene were identified in 40-60% of the tumors investigated, suggesting a driver role for FGFR1 signaling in TIO tumorigenesis (4, 5). Thus, it was hypothesized that an FGFR inhibitor may be effective therapy and possibly tumoricidal in TIO.

BGJ398 belongs to the pyrimidinyl aryl urea chemical class and its chemical name is 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-{6-[4-(4-ethyl-1-piperazin-1-yl)phenylamino]-pyrimidinyl-4-yl}-1-methylurea phosphate(1:1). It is an orally bio-available, selective and ATP competitive pan-fibroblast growth factor receptor (FGFR) kinase inhibitor which has demonstrated anti-tumor activity in preclinical, in vitro and in-vivo tumor models harboring FGFR genetic alterations and in cancer patients with tumors which harbor oncogenic FGFR genetic alterations, including gene fusions. Additionally, elevation of blood phosphorus is an observed pharmacodynamic effect of BGJ398 in treated patients with non-FGF23 producing solid tumors.

Early results of BGJ398 treatment of a patient with widely metastatic TIO harboring the FN1/FGFR1 translocation show very promising results (6). Treatment was associated with: dramatic disappearance of many metastases on FDG-PET/CT, marked decrease in blood FGF23 levels, resolution of hypophosphatemia with intermittent, dose-dependent hyperphosphatemia, and differentiation of malignant TIO to mature, remodeling lamellar bone on pre- and post-treatment biopsies. A second patient with TIO due to a non-localizable tumor has also been treated with BGJ398 for several months with similar decreases in FGF23 and normalization of blood phosphate levels while on drug. Thus, BGJ398 for the treatment of TIO is an excellent example of molecularly targeted approach to personalized medicine and a promising treatment for TIO.

# 2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

## 2.1 ELIGIBILITY CRITERIA

### 2.1.1 Inclusion Criteria

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

1. Aged 18-85 years

2. Diagnosis of TIO due to a non-localized or unresectable tumor, or metastatic disease or resectable tumor that cannot be removed by minor surgical procedure. This diagnosis will be confirmed prior to enrollment on protocol 01-D-0184. Where clinically indicated, genetic testing to rule-out heritable causes of FGF23 excess will also be performed on 01-D-0184.
3. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.
4. Able to swallow and retain oral medication.
5. Able to provide informed consent

### 2.1.2 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Have another genetic or secondary cause of hypophosphatemia.
2. History of any other malignancy that has not been cured/in remission for 5 years.
3. Patients who previously received treatment with an FGFR inhibitor other than BGJ398.
4. Current evidence of corneal or retinal disorder/keratopathy including, but not limited to: bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjuctivitis, confirmed by ophthalmologic examination
5. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BGJ398 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection)
6. Patients who are currently receiving treatment with agents that are known strong inducers or inhibitors of CYP3A4 are prohibited. This includes treatment with enzyme-inducing antiepileptic drugs including carbamazepine, phenytoin, phenobarbital, and primidone.
7. Consumption of grapefruit, grapefruit juice, pomegranates, star fruits, Seville oranges or products within 7 days prior to first dose
8. Use of amiodarone within 90 days prior to first dose
9. Current use of therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulants. Heparin and/or low molecular weight heparins are allowed.
10. Insufficient bone marrow function defined as all of the following:
    - ANC <1,500/$mm^3$ [1.0 x $10^9$/L] AND
    - Platelets < 75,000/$mm^3$ [75 x $10^9$/L] AND
    - Hemoglobin < 10.0 g/dL
11. Insufficient hepatic and renal function defined as one of the following:
    - Total bilirubin > 1.5x ULN OR
    - AST/SGOT and ALT/SGPT > 2x ULN OR
    - Blood creatinine > 1.5xULN and/or calculated eGFR < 45 ml/min/1.73 m2 (calculated by CKD-Epi)
12. Clinically significant cardiac disease including any of the following:
    - Congestive heart failure requiring treatment (NY Heart Association grade ≥ 2),
    - 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
- QTcF > 450 msec (males); > 470 msec (females)
- History of congenital long QT syndrome

13. Recent (≤3 months) transient ischemic attack or stroke
14. Patients under age 21 will have a bone age assessed as part of their clinically indicated skeletal survey under 01-D-0184 and will not be offered enrollment if their growth plates are open.
15. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
16. 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 subject. 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 subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - Combination of the following (a+b or a+c, or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

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 or 6 months of spontaneous amenorrhea with serum FSH >40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.

Sexually active males unless they use a condom during intercourse while taking drug and for 3 months after the last dose of the study drug and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

Patients with TIO who are currently taking BGJ398 or have been treated with BGJ398 in the past are eligible to participate in this study, provided that they discontinue BGJ398 for 2 weeks prior to the baseline visit.

### 2.1.3 Recruitment Strategies

It is estimated that new patient accrual will take approximately 2 years. Recruitment strategies may include IRB-approved advertising and direct contact with healthcare providers. Interested individuals may contact the NIH *Office of Patient Recruitment Clinical Research Center* via a toll-free telephone number (800-411-1222) or email (prpl@mail.cc.nih.gov) to be prescreened for the protocol using questions provided by the research team. Individuals who are deemed eligible by the patient recruitment staff will have their contact information forwarded to the study staff. Because of the frequency of visits to the NIH, subjects will be limited to the individuals living within North America.

## 2.2 SCREENING EVALUATION

### 2.2.1 Pre-Screening

Potential subjects will be asked to arrange for a referral letter from their local physician and a copy of their medical records to be sent to the clinical site. Based on a review of their medical records, further qualified subjects will be enrolled and evaluated on the Evaluation of Bone and Mineral Disorders protocol (01-D-0184), to exclude genetic causes of FGF23-mediated hypophosphatemia and confirm the diagnosis of TIO, and ensure that the tumor cannot be localized and/or easily resected.

### 2.2.2 Screening Visit

Patients with a confirmed diagnosis of inoperable, metastatic, or non-localized TIO will be enrolled into this protocol by agreeing to and signing the informed consent and will undergo further eligibility screening (thoroughly evaluated based on the inclusion and exclusion criteria) at the NIH Clinical Center. This may be done as an inpatient or outpatient visit, at the discretion of the investigator and the subject. If eligible and the patient would like to begin drug immediately, the testing for the screening and baseline visits will be combined into a single inpatient visit. If not, the baseline visit and initiation of drug should occur within 6 weeks of the screening visit. Patients who have been previously treated with BGJ398 must be off BGJ398 for at least 2 weeks prior to the screening/baseline visit.

Procedures and tests during screening (if not combined with baseline visit) will include:

1. History
    a. Detailed history of disease
    b. Current medications including assessment of exclusionary medications/foods
2. Physical Exam
    a. Height and weight measurement
    b. Vital signs (pulse, blood pressure, temperature, and respiratory rate)
    c. Physical examination
3. Blood tests
    a. Blood chemistries: sodium, potassium, chloride, bicarbonate, creatinine, glucose, urea nitrogen, albumin, calcium, magnesium, phosphorous, alkaline phosphatase,

alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, LD, total protein, total CK, and uric acid

b. Thyroid Stimulating Hormone (TSH) and Free Thyroxine (fT4)
c. 25-OH vitamin D, 1,25 $(OH)_2$ -Vitamin D, intact PTH and FGF23 levels.
d. Complete blood count (CBC): white blood cells (WBC), red blood cells (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), red cell distribution width (RDW), and platelets.

4. Urine testing
   a. Urine pregnancy test in females with childbearing potential.
   b. Urinalysis: glucose, protein, urobilinogen, pH, hemoglobin, ketones, nitrite, leukocyte esterase, appearance, specific gravity, color, RBC, WBC, and squamous cells.
   c. 24-hour urine for calcium, phosphorus, creatinine.
5. Imaging
   a. FDG or $^{68}$Ga-DOTATATE PET/CT or Octreotide SPECT/CT if adequate study not done within the preceding 6 months.
6. Electrocardiogram to rule out exclusionary rhythm abnormalities.

## 2.3 REGISTRATION PROCEDURES

### 2.3.1 For Participating Site Registration: NOT APPLICABLE.

## 2.4 RANDOMIZATION (OR STRATIFICATION) PROCEDURES: NOT APPLICABLE.

## 2.5 BASELINE EVALUATION (MAY BE COMBINED WITH SCREENING VISIT):

Subjects who elected not to initiate BGJ398 at the screening visit will return to the NIH for an inpatient admission within 6 weeks of the screening visit to begin BGJ398 treatment. At that time, the following procedures and tests will be performed prior to the first dose:

1. History
   a. Interim history
   b. Current medications
2. Physical Exam
   a. Weight and height measurement
   b. Arm span and sitting height will be measured at baseline and 24-week visits
   c. Vital signs (pulse, blood pressure, temperature, and respiratory rate)
   d. Physical examination
3. Blood tests
   a. Blood chemistries: sodium, potassium, chloride, bicarbonate, creatinine, glucose, urea nitrogen, albumin, calcium, magnesium, phosphorous, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, LD, total protein, total CK, 25 OH vitamin D and uric acid

   b. Complete blood count (CBC): white blood cells (WBC), red blood cells (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), red cell distribution width (RDW), and platelets.
   c. Bone turnover markers - collagen type I C-telopeptide (CTX) and Procollagen I Intact N-Terminal (P1NP) (baseline, 12-week, 24-week, 36-week visits)
   d. 25-OH-Vitamin D (baseline, 24-week, and 36-week visits)
   e. 1,25-$OH_2$-Vitamin D, intact PTH, FGF23
   f. Two-hour oral glucose tolerance test (baseline and 8-week visit)
4. Urine testing
   a. Urine pregnancy test in females with childbearing potential.
   b. Urinalysis: glucose, protein, urobilinogen, pH, hemoglobin, ketones, nitrite, leukocyte esterase, appearance, specific gravity, color, RBC, WBC, and squamous cells.
   c. 24-hour urine for calcium, phosphorus, creatinine (at monthly NIH visits)
   d. Spot urine for calcium, phosphorus, creatinine (local laboratory visits only)
5. Imaging
   a. Renal ultrasound (baseline and 24-week visit)
   b. Echocardiogram (baseline, 8-week, and 24-week visit) Patients with a decline in ejection fraction will be monitored monthly with serial echocardiograms for resolution.
6. Electrocardiogram (EKG) (screening and every 4-12 weeks depending on risk factors for long QTc)
7. Questionnaires (described in section 3.5)
   a. RAND SF36
   b. PROMIS
8. Rehabilitation Medicine Consultation
   a. The Five Times Sit to Stand Test (lower extremity strength)
   b. The grip strength test (hand dynamometer; upper extremity strength)
   c. The Disabilities of Arm Shoulder and Hand Outcome Measurement (DASH).
   d. Clinical rehabilitation evaluation (baseline, 24-week, and 36-week visits)
   e. Six-minute walk test (baseline, 24-week, and 36-week visits)
9. Placement of an indwelling catheter for frequent blood draws (baseline visit only)
10. Ophthalmology Evaluation (baseline, monthly NIH visits while on BGJ398, 36-week, and as clinically indicated)
11. With the first dose (time 0), the following tests are performed within the first 24 hours (baseline visit only):
   a. Blood draw at time 0 and every 2 hours (± 20 minutes) for phosphorous and creatinine
   b. Spot urine at time 0 and every 2 hours (± 20 minutes) for phosphorus and creatinine
   c. Blood draw at time 0 and every 4 hours (± 20 minutes) for FGF23, 1, 25 $(OH)_2$-vitamin D, ionized calcium, iPTH.

d. Blood draw for pharmacokinetics at time 0 and 2, 4, 6, 8, 10 and 24 hours (± 20 minutes) after the first dose.

All tests and procedures performed at the baseline visit will be repeated at the interval visits unless noted above. Pharmacokinetic samples will be repeated with fasting labs at the 4-week and 8-week visit. In patients with identifiable tumors and/or metastatic disease, the imaging study that best characterized their tumor(s) prior to BGJ398 will be repeated at the 24-week visit, if clinically indicated. See schedule of events in section 3.6.1 for more details.

# 3 STUDY IMPLEMENTATION

## 3.1 STUDY DESIGN

Calcitriol (half-life is 5-8 hour) and phosphorous will be withheld for 3 days prior to the initiation of BGJ398 to allow for washout.

After initiation of study drug, subject will complete 24 weeks of BGJ398 with escalation/de-escalation of drug as described in Sections 3.1.2 and 3.3. Patients will return to the NIH every 4 weeks while on BGJ398 for an outpatient visit and labs per the schedule of events. Between monthly NIH visits, labs will be obtained per the schedule of events at the patients' local laboratories and results will be forwarded to the study team for review. In addition, any patient taking a concomitant medication associated with prolonged QT will obtain an EKG as an outpatient within 7-10 days after an increase in BGJ398 or the relevant concomitant medication. At the end of 24th week of BGJ398 treatment, subjects will be admitted as inpatients at the NIH for detailed laboratory and imaging evaluation as described in schedule of events. At the completion of the 24 weeks of treatment, patients who appear to have had a complete metabolic response will be evaluated at the NIH every 4 weeks for 3 additional visits. Complete metabolic response will be defined as normalization of blood phosphate and FGF23 levels after withdrawal of study drug. Local labs will be obtained in between NIH visits as clinically indicated on an as-needed basis. Subjects who have normal phosphate levels while on BGJ398 but have not had a complete metabolic response at the end of the 24 weeks of study drug may be considered for drug continuation in the extension phase, described in 3.1.3. Those who have not responded, have experienced significant side effects, or do not want to continue in the extension phase, will be terminated from the study and referred for other treatment.

During the active drug study period, subjects will not receive calcitriol and phosphorous supplements. However, subjects may be placed on calcitriol and phosphorous while in the post-BGJ398 drug monitoring phase or during dose interruptions, as clinically indicated. During the post-drug monitoring period calcitriol and phosphorous will be re-started on individual basis as clinically indicated (muscle weakness, bone pain, hypophosphatemia).

### 3.1.1 Drug-related adverse events (DRAE)

Drug-related adverse events (DRAE) will be defined as an AE or clinically significant abnormal laboratory value suspected to be related to therapy with BGJ398 (i.e., assessed as unrelated to disease progression, intercurrent illness, or concomitant medications), including those AEs and abnormal laboratory values that result in failure to meet the criteria for re-treatment or to begin a new cycle of therapy.

The criteria for defining DRAE are listed in (Table 3-1) using CTCAE v4.0.

Patients who experience a DRAE will have their therapy with BGJ398 interrupted and will be followed until the toxicity has resolved to CTCAE grade ≤ 1 or to the patient's baseline value. After recovery from the toxicity in question, if the investigator believes that it is in the patient's best interest to resume therapy with BGJ398, the patient may resume therapy at a lower dose level.

Prior to enrolling patients into a higher dose level, Grade ≥ 2 adverse events should be reviewed for all patients at the current dose level.

Table 3-1 Criteria for defining dose-modifications/interruptions for adverse events

| **TOXICITY** | **DRAE CRITERIA** |
|---|---|
| Skipped/ delayed dose | The inability to administer BGJ398 on ≥ 75% of scheduled treatment days during cycle 1 (i.e. ≥ 21 days for a 28-days daily dosing schedule) due to unresolved adverse event of any grade and considered at least possibly, probably or definitely related to the study drug.<br>Delay in 2nd cycle administration due to failure of recovery from a possibly, probably or definitely related adverse event to grade ≤ 1 or baseline by Day 43 (D28 of cycle 1 + 15 days), except for alopecia. |
| Blood/ bone marrow | Febrile neutropenia CTCAE Grade ≥ 3.<br>Neutropenia CTCAE Grade > 3 for > 7 consecutive days.<br>Thrombocytopenia<br><br>- CBC abnormalities CTCAE Grade 3 for > 7 consecutive days and/or with signs of clinically significant bleeding.<br><br>-CBC abnormalities CTCAE Grade 4.<br>Anemia CTCAE Grade 4. |
| Renal/ genitourinary | Creatinine CTCAE Grade 1 for > 7 consecutive days and blood Pi > 5.5 mg/dL and/or blood tCa x Pi > 55 $mg^2/dL^2$ and despite phosphorus lowering therapy for at least 14 days.<br>Creatinine CTCAE Grade 2 for > 7 consecutive days.<br>Creatinine CTCAE Grade ≥ 3. |
| Hepatic | Bilirubin CTCAE Grade 2 for > 7 consecutive days.<br>Bilirubin CTCAE Grade ≥ 3.<br>AST or ALT CTCAE Grade ≥ 3. |
| Pancreas | Pancreatitis CTCAE grade ≥ 2. |

| TOXICITY | DRAE CRITERIA |
|---|---|
| | Amylase/lipase (blood-high)<br><br>-CTCAE Grade ≥ 3 asymptomatic amylase and/or asymptomatic lipase not reversible to CTCAE Grade ≤ 2 within 7 days. |
| Cardiac | QTcF interval > 500ms.<br>Other CTCAE Grade ≥ 3. |
| Constitutional | Fatigue CTCAE Grade 3 for > 7 consecutive days.<br>Fatigue CTCAE Grade 4. |
| Ocular/visual | Clinical evidence of corneal disorder/retinal disease of any grade (CTCAE grade ≥ 1) including but not limited to corneal edema, abrasion, bullous/band keratopathy, inflammation/ ulceration, keratoconjunctivits confirmed by ophthalmologic examination during any cycle.<br>Any other ocular/visual toxicity CTCAE Grade ≥ 3. |
| Gastrointestinal | CTCAE Grade 3 or 4 nausea/vomiting and/or diarrhea despite the use anti-emetic and anti-diarrhea therapy, respectively. |
| Metabolic/ laboratory | Hyperphosphatemia (blood-high)<br>-Blood Pi > 7.0 mg/dL for > 7 consecutive days despite phosphorus lowering therapy for at least 14 days.<br><br>-Blood Pi > 9.0 mg/dL, despite phosphorus lowering therapy for at least 14 days.<br><br>-Blood Pi > 10.0 mg/dL<br><br>Hypercalcemia (blood-high)<br>-Blood calcium CTCAE Grade 2 for > 7 consecutive days.<br><br>-Blood calcium CTCAE Grade ≥ 3. |
| Other | Clinical evidence for any grade (CTCAE Grade ≥ 1) of ectopic, *de-novo*-calcification within the soft tissue including the peri-articular spaces and vascular as well as visceral tissues (e.g. kidney, lung, stomach, myocard, etc.)<br><br>Any other CTCAE Grade 3 or 4 non-hematological toxicity except with following exclusions:<br><br>-Alkaline phosphatase CTCAE Grade ≥ 3.<br><br>-Lymphocytopenia CTCAE Grade ≥ 3 unless considered clinically significant. |

### 3.1.2 Dose Escalation

The starting dose of BGJ398 for all subjects not previously treated with BGJ398 will be 75 mg. This dose was based on studies investigating this drug's use in subjects with cholangiocarcinoma, as well as our two patients with TIO who have been treated on Novartis' signature trial. Patients previously treated with BGJ398 will be started on the last dose that they were taking prior to enrolling in this study, based on prior tolerability. While the two NIH patients treated on the Novartis Signature trial (6-9) were treated with 3 weeks on BGJ followed by 1 week off BGJ per cycle, our observations that hyperphosphatemia did not develop in these two subjects suggest that continuous BGJ therapy may be more efficacious in this population. Therefore, subjects will be treated with continuous BGJ398 therapy for six 28-day cycles. FGF23 levels will be measured every 2 weeks. If the FGF23 levels are not suppressed to less than 100 RU/ml on the 6-week outpatient labs, the dose of BGJ398 will be increased to 100 mg once daily after the 8-week NIH visit. The increased dose (100 mg) will be maintained for next 8 weeks. If the FGF23 levels continue to be greater than or equal to 100 RU/ml on the 14-week outpatient labs, the dose of BGJ398 will be increased to 125 mg daily after the-16 week NIH visit for the next 8 weeks. If a subject experiences a significant toxicity (DRAE), the medication will be held and restarted at the previous dose as described in section 3.1.1.

Sample dose modification table:

| **Dose Escalation Schedule** | |
|---|---|
| **Dose Level** | Dose of BGJ398 |
| Level 1 | 75 mg |
| Level 2 | 100 mg |
| Level 3 | 125 mg |

### 3.1.3 Extension Phase

Subjects who do not demonstrate complete metabolic response at the end of the 1 week end-of study pharmacodynamic period (see section 3.4) following 24 weeks of treatment or at any time during the follow-up period will be offered the opportunity to resume study drug at the maximum tolerated dose if they experienced normalization of blood phosphate levels while on BGJ398. They will be allowed to continue until either study closure, patient withdrawal, or, if in the judgement of the investigator, the adverse event profile of the subject outweighs the benefit. Subjects will continue to be monitored monthly for efficacy and safety. This will include monthly telephone follow-up to assess adverse events, monthly laboratory assessments and outpatient NIH visits at a minimum of every three months, to include an ophthalmologic examination.

### 3.2 DRUG ADMINISTRATION

BGJ398 will be dispensed at the start of each 28-day cycle. Patients will self-administer BGJ398 at home after the initial dose(s) are given during the inpatient period. All patients must return their bottle(s) of BGJ398 at the appropriate scheduled visit. Study site staff will monitor subject compliance assessed by the capsule count. Subjects will be instructed to notify study site personnel of any missed doses.

The following general guidelines should be followed for BGJ398 administration:

- Patients should be instructed to take the daily dose of BGJ398 in the morning, at approximately the same time each day (24 ± 2 hr interval).
- BGJ398 should be administered in the fasted state, at least 1 hour before or 2 hours after a meal.
- BGJ398 should be taken with a large glass of water (~250 mL) and consumed over as short a time as possible. Patients should be instructed to swallow the correct number of 25 mg or 100 mg capsules comprising the appropriate dose whole and not chewed, crushed, dissolved or divided.
- If the patient forgets to take the scheduled dose in the morning, he/she should not take the dose more than 2 hours after the usual time. If the time extends 2 hours or more, the dose should not be taken (missed). Any doses that are missed should be skipped altogether and should not be replaced or made up at the next scheduled dosing. The scheduled dose should be taken the next day.
- If vomiting occurs following the dosing of study drug, re-dosing is not permitted that same day. Dosing should resume the next day. This event needs to be noted appropriately.
- BGJ398 is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of both compounds, and limit bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. Therefore, BGJ398 should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.
- Patients must avoid consuming Seville (blood) oranges or juice, grapefruit, grapefruit juice, grapefruit hybrids, or pomelos from 7 days prior to the first dose of study medication through the end of study participation. This is due to a potential CYP3A4 interaction with study medication. Normal oranges and orange juice are allowed.

### 3.3 DOSE MODIFICATIONS

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted to allow the patient to continue the study treatment. The following guidelines need to be applied:

- These changes must be recorded in the patient's medical records and eCRF.
- All dose modifications should be based on the worst preceding toxicity.

- Following resolution of toxicity to baseline or ≤ grade 1, treatment is resumed at lower dose of study drug as per Table 3.3.1. If treatment is resumed at the lower dose of study drug, and the same toxicity recurs with the same or worse severity, the patient must discontinue study treatment.

Table 3.3.1 Dose reduction table:

| BGJ398 dose level | BGJ398 dose |
|---|---|
| Starting level (0) | 75 mg po once daily |
| Dose level-1 | 50 mg po once daily |
| Dose level-2 | 25 mg po once daily |

### 3.4 END OF STUDY PHARMACODYNAMICS:

After the last dose is administered (24-week timepoint), the subject will be seen at the NIH and following labs will be done daily (± 1 day) for up to 7 draws to evaluate for end-of-study pharmacodynamics.

- Blood FGF23
- Blood 1, 25 $(OH)_2$-Vitamin D
- Blood Phosphorous, Calcium, and Creatinine
- Blood PTH
- Urine Calcium, Creatinine, and Phosphorous.

### 3.5 QUESTIONNAIRE

**RAND® Medical Outcomes Short Form Survey Instrument (SF-36) Version 1.0**

RAND Medical Outcomes Short Form Survey Instrument (SF-36) Version 1.0 will be used as a secondary outcome measure to determine effects of BGJ398 on Health-Related Quality of Life (HRQOL) over the duration of the study. The RAND® 36-Item Health Survey is a generic validated instrument used to measure (HRQOL) parameters of physical and mental health across age, disease, and treatment groups in individuals 18 years and older. The questionnaire is a multi-purpose self-reported health assessment tool composed of 36 questions in eight different domains that examine aspects of physical and mental health from the patient's point of view. This short questionnaire will be administered in paper or electronic form and completed by the patients at baseline and then monthly for the duration of the study. The average duration of time for completion of the questionnaire is 5-10 minutes. Completed paper versions of the survey will be coded with the subject number and kept in a binder in a locked office. Data collected by means of an electronic tablet

will be identifiable only by the patient's code. The survey uses norm-based scoring. Surveys from RAND® Health are public documents, available without charge.

Survey and scoring tools can be found at:

https://www.rand.org/health/surveys_tools/mos/36-item-short-form.html

**Patient-Reported Outcomes Measurement Information System (PROMIS®)**

PROMIS item banks (questionnaires) will be used as a secondary outcome measures to determine effects of BGJ398 on pain, fatigu and mobility over the duration of the study. PROMIS item banks are self-report validated outcome measurement tools used to evaluate and monitor physical, mental and social health in adults (and children) with uses in the general population and in individuals living with chronic conditions. The adult item banks for fatigue (8 questions), mobility (15 questions), pain interference (40 questions) will be administered either on paper, by computer or with an iPad app. Completed paper versions of the survey will be coded with the subject number and kept in a binder in a locked office. The average duration of time for completion of all 3 item banks is approximately 30 minutes. Item banks and scoring instructions can be found at: http://www.healthmeasures.net/explore-measurement-systems/promis

## 3.6 STUDY CALENDAR

### 3.6.1 Schedule of Events:

| | **Prescreen** | **Screen** | **V0** | **V 1** | **V 2** | **V 3** | **V 4** | **V 5** | **V 6** | **V 7** | **V 8** | **V 9** | **V 10** | **V11** | **V12** | **V13** | **V 14** | **V 15** | **V 16** | **V1 7** | **V 18** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Target Date (weeks)** | | (-)0-6 | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 |
| **Visit Window (days)** | | ±4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 |
| **Recruitment and Enrollment** | | | | | | | | | | | | | | | | | | | | | |
| Telephone Pre-Screening | X | | | | | | | | | | | | | | | | | | | | |
| Informed Consent [1] | | X | | | | | | | | | | | | | | | | | | | |
| Inpatient NIH visit^ | | | X | | | | | | | | | | | | X[$] | | | | | | |
| Outpatient NIH visit | | X | | | X | | X | | X | | X | | X | | X[$] | | X | | X | | X |
| Outside lab draw* | | | | X | | X | | X | | X | | X | | X | | | | | | | |
| BGJ398[#] | | | X | | X | | X | | X | | X | | X | | X | | | | | | |
| **Medical History** | | | | | | | | | | | | | | | | | | | | | |
| Medical History | | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| RAND SF-36 | | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| Concomitant Medications | | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |

| | Prescreen | Screen | V0 | V 1 | V 2 | V 3 | V 4 | V 5 | V 6 | V 7 | V 8 | V 9 | V 10 | V11 | V12 | V13 | V 14 | V 15 | V 16 | V1 7 | V 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Target Date (weeks)** | | (-)0-6 | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 |
| **Visit Window (days)** | | ±4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 |
| Adverse Events | | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| **Fitness Measures/Rehab questions** | | | | | | | | | | | | | | | | | | | | | |
| PROMIS | | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| 6-Minute Walk Test | | | X | | | | | | | | | | | | X | | | | | | X |
| Five times sit and stand test | | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| Grip strength test | | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| DASH^^ | | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| Clinical rehab evaluation | | | X | | | | | | | | | | | | X | | | | | | X |
| **Physical Exam** | | | | | | | | | | | | | | | | | | | | | |
| Height/weight | | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| Sitting height<br>Arm span | | | X | | | | | | | | | | | | X | | | | | | |
| Vital Signs | | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| Physical Examination | | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| **Blood Tests** | | | | | | | | | | | | | | | | | | | | | |
| Every 2 hours (± 20 minutes) for Pi and Cr | | | X | | | | | | | | | | | | | | | | | | |
| Blood every 4 hours for FGF23, 1, 25D, iCa, iPTH. | | | X | | | | | | | | | | | | | | | | | | |
| Blood FGF23, 1,25D, Pi, Ca, Cr, eGFR, and iPTH (7±1 daily) | | | | | | | | | | | | | | | X[$] | | | | | | |
| 2-hour Oral Glucose Tolerance Test | | | X | | | | X | | | | | | | | | | | | | | |
| Hepatic panel | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| Acute care panel, eGFR and CBC | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| Mineral panel (Ca, Mg, Phos, Alb) | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| TSH and Free T4 | | X | X | | | | | | | | | | | | X | | | | | | X |
| 25-OH-Vitamin D | | X | X | | | | | | | | | | | | X | | | | | | X |
| Intact PTH | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| 1,25 $(OH)_2$ vitamin D | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| P1NP | | | X | | | | | | X | | | | | | X | | | | | | X |
| CTX | | | X | | | | | | X | | | | | | X | | | | | | X |
| Research bloods for FGF23 | | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |

| | Prescreen | Screen | V0 | V 1 | V 2 | V 3 | V 4 | V 5 | V 6 | V 7 | V 8 | V 9 | V 10 | V11 | V12 | V13 | V 14 | V 15 | V 16 | V1 7 | V 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Target Date (weeks)** | | (-)0-6 | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 |
| **Visit Window (days)** | | ±4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 | ± 4 |
| FGF23 (Mayo) | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | | X | | X |
| BGJ398 - PK Testing | | | X | | X | | X | | | | | | | | | | | | | | |
| **Urine testing** | | | | | | | | | | | | | | | | | | | | | |
| Urine every 2 hours (± 20 minutes) for Pi and Creatinine | | | X | | | | | | | | | | | | | | | | | | |
| Spot urine Pi, Ca, creatinine | | | | X | | X | | X | | X | | X | | X | X[$] | | | | | | |
| Urine Pregnancy test (if indicated) | | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| Urinalysis | | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| 24-hour Ca, Pi, creatinine | | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X |
| **Consults and imaging testing** | | | | | | | | | | | | | | | | | | | | | |
| Ophthalmology evaluation (monthly while on BGJ398) | | | X | | X | | X | | X | | X | | X | | X | | | | | | X |
| Nuclear medicine studies (if not done in last 6 mos – repeated at 24 weeks in those with identified tumors) | | X | | | | | | | | | | | | | X | | | | | | |
| Electrocardiogram (every 4-12 weeks as indicated) | | X | | | | | | | | | | | | | | | | | | | |
| Echocardiography | | | X | | | | X | | | | | | | | X | | | | | | |
| US kidney | | | X | | | | | | | | | | | | X | | | | | | |

[^] At the inpatient visit (during the first drug administration), blood and urine will be collected every 2 hours (± 20 minutes) for 24 hours to measure phosphorous and TRP and every 4 hours to measure FGF23, intact PTH, ionized calcium, 1, 25 (OH)2 vitamin D.

^^ DASH: The Disabilities of Arm Shoulder and Hand Outcome Measurement

# BGJ398 is administered during the first in patient visit. The patient will be supplied with the drug every 4 weeks for total of 6 months. The patient will be started on 75 mg dose and the dosage changes will be made based on the adverse events and response as described in the protocol.

*Outside labs may be done at NIH or at outside lab based on patient convenience.

[$] V12 (24-weeks) may be done as an inpatient or outpatient visit based on patient convenience. Labs are drawn at the NIH daily (±1 day) for total of 7 lab draws for blood FGF23, 1- 25 $(OH)_2$-Vitamin D, Phosphorous, Calcium, Creatinine and iPTH, Urine Calcium, Creatinine, and Phosphorous.

## 3.7 SURGICAL GUIDELINES: NOT APPLICABLE

## 3.8 RADIATION THERAPY GUIDELINES: NOT APPLICABLE

## 3.9 COMPENSATION: NOT APPLICABLE

## 3.10 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

### 3.10.1 Criteria for permanent removal from protocol therapy

Subjects will be informed that they may choose to withdraw or the investigator may remove them from BGJ398 if it is in their best interest or if the subjects are unable to complete the required assessments and/or treatment. Voluntary withdrawal from the protocol is always an option for research participants.

The following conditions will require the permanent withdrawal of a subject from the BGJ398 therapy:

- Pregnancy
- Decline in calculated GFR to $\leq$ 25 mL/min/1.73 m2 or decline in calculated GFR by 25 mL/min/1.73m2 without clear etiology that persists on three monthly measurements (measured at the NIH or the subject's local laboratory).
- CTCAE ≥ Grade 4 abnormalities in hepatic transaminases (ALT and AST)
- Treatment failure as defined by a blood phosphorus level below the lower limit of normal while taking the maximum tolerated dose of BGJ398 on two consecutive cycles.
- Investigator judgment based on subject's best medical interest

Subjects who require permanent discontinuation of BGJ398 therapy due to an adverse event will continue to be followed in the study until the toxicity has resolved or up to 30 days after study drug discontinuation. Pregnancies will be recorded from the time written informed consent is obtained until the subject is withdrawn from the study. Subjects who become pregnant during the study will be taken off BGJ398 and will be followed (with the subject's permission) until a pregnancy outcome is reached. The subjects will be referred to a physician outside of NIH for care. If the pregnancy results in anything other than a normal birth or elective abortion of a healthy fetus, it will be reported as an SAE. At the end of the pregnancy follow-up period, the subjects will be withdrawn from the trial.

Off-Study Criteria

- Screen failure including meeting one of the exclusion criteria that cannot be resolved within 6 weeks of the screening visit.
- Subject noncompliance with study procedures.
- Completed study follow-up period.
- Participant requests to be withdrawn from study.
- Investigator judgment based on subject's best medical interest.

- Death.

### 3.10.2 Off-Study Procedure

Once the decision is made to take a patient off the study protocol, a note will be entered into CRIS. The subject(s) will be referred back to their local physician(s). With written consent from the subject(s), referring physicians will receive clinical information about the health status of subjects when they are taken off the study protocol.

## 4 CONCOMITANT MEDICATIONS/MEASURES

The patient must notify the investigational site at the time of starting any new medications he/she takes after the start of the study drug. All medications (other than study drug) administered during the study must be listed on the Concomitant Medications Form in the eCRF.

### 4.1 PERMITTED CONCOMITANT THERAPY REQUIRING CAUTION AND/OR ACTION

### 4.1.1 Drugs that alter the pH of the GI tract

BGJ398 is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of both compounds, and limit bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. Therefore, study drug(s) should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.

Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to induce CYP3A enzymes, thereby increasing the risk of reducing drug exposure to sub-therapeutic levels. In addition, BGJ398 is an in vitro inhibitor of CYP3A4 and has the potential to increase the systemic exposure of corticosteroids that are metabolized by CYP3A4.

Systemic corticosteroid treatment can be used with caution.

### 4.1.2 CYP substrates and inhibitors

BGJ398 was shown to inhibit the cytochrome p450 isoenzyme CYP3A4 in *in-vitro* assays, thus, suggesting an increased risk of drug interactions with concomitant medications that are metabolized by CYP3A4. However, such interactions have not been confirmed in patients. Therefore, investigators may administer medications that are known to be metabolized by CYP3A4. Patients must be monitored for potentiation of toxicity and may require dose titration or reduction of the CYP3A4 substrate. In particular caution is advised when substrates with a narrow therapeutic index, such as alfentanil, fentanyl, astemizole, cisapride, diergotamine, ergotamine, pimozide, quinidine, sirolimus, tacrolimus, and terfenadine need to be administered. Please refer to the following website http://medicine.iupui.edu/clinpharm/DDIs/table.asp for a more complete list of the substrates of CYP3A4.

Hormonal contraceptives may be affected by cytochrome P450 interactions and are therefore not considered effective for this study when used alone. Highly effective contraception as defined in the exclusion criterion should be maintained throughout the study. Additionally, BGJ398 may increase the systemic exposure of ethinyl estradiol, so patients on oral contraception should be appropriately monitored for side effects.

BGJ398 is a reversible inhibitor of CYP2C8, CYP2C9 and CYP2C19. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2C8, CYP2C9, CYP2C19, or those substrates that have a narrow therapeutic index. BGJ398 is a substrate of CYP3A4. Therefore moderate inhibitors and inducers should be used with caution if no other alternative is available.

### 4.1.3 Transporter substrates

*In vitro* data show that BGJ398 is an inhibitor of BCRP. CQM157, a metabolite of BGJ398, is an inhibitor of transporters P-gp, BCRP, OATP1B1, and OATP1B3 ($IC_{50}$ 2-4 μM). In the absence of data confirming whether such interactions occurs in patients receiving such medications must be monitored for potential toxicity and may require dose titration or reduction of the medication.

### 4.1.4 Anti-emetics

Anti-emetics are allowed for the treatment of nausea or vomiting. It is recommended to avoid using drugs that are known to cause QT prolongation. Note that some anti-emetics have a known risk for Torsade do Pointes, and therefore need to be used with caution. Aprepitant is both a sensitive substrate and a moderate CYP3A4 inhibitor and should be used with caution if an alternative is not available.

### 4.1.5 QT/QTc interval prolongation or torsade de pointes medications

Medications that have the potential to prolong the QT/QTc interval or induce torsade de pointes are allowed with caution. Investigators at their discretion may co-administer such medications, as listed below, but patients should be carefully monitored. Any patient taking a concomitant medication associated with prolonged QT will obtain an EKG as an outpatient within 7-10 days after an increase in BGJ398 or the relevant concomitant medication.

a. Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
b. Class III antiarrhythmics (e.g., sotalol, ibutilide)
c. Class 1C antiarrhythmics (e.g., flecainide, propafenone)
d. Antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol)
e. Antidepressants (e.g., fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants e.g. amitriptyline, imipramine, maprotiline)
f. Opioids (e.g., methadone)
g. Macrolide antibiotics & analogues
h. Quinolone antibiotics (e.g., moxifloxacin, gatifloxacin)
i. Pentamidine
j. Antimalarials (e.g., quinine)
k. Azole antifungals (e.g., voriconazole)

l. Domperidone
m. 5-HT3 antagonists (e.g., dolasetron)
n. Beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

## 4.2 PROHIBITED CONCOMITANT THERAPY

### 4.2.1 Other investigational and antineoplastic therapies

Other investigational therapies must not be used while the patient is on the study. Anticancer therapy other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the study.

### 4.2.2 CYP inhibitors

Strong inhibitors of CYP3A4, as listed below, are prohibited because BGJ398 is a likely substrate of this isoenzyme. Caution should be used during administration of moderate inhibitors. Please note that the list may not be comprehensive. In addition, the following food products are prohibited: Seville oranges or juice, grapefruit, grapefruit juice, grapefruit hybrids, and pomelos.

a. Anti-fungal agents: Ketoconazole, itraconazole, fluconazole
b. Anti-retroviral agents: Ritonavir, nelfinavir, indinavir, saquinavir, amprenavir, atazanavir, fosamprenavir
c. Antibiotic agents: Clarithromycin, telithromycin, erythromycin
d. Others: Aprepitant, diltiazem, verapamil, nefazodone, grapefruit juice

Patient on strong or moderate CYP3A4 inducers or inhibitors or medications that rely on CYP3A4 for metabolism, should switch whenever possible to a product with less interaction with/reliance on the pathway or patient should be on a stable dose of the medication prior to enrollment

### 4.2.3 CYP inducers

Strong inducers of CYP3A4 are prohibited because their usage would likely decrease the exposure of BGJ398. Caution should be used during administration of moderate inhibitors.

### 4.2.4 Phosphorus and calcium

Prior to initiation of BGJ398, TIO will be managed with phosphate supplements and calcitriol, with the addition of vitamin D and calcium supplements as clinically indicated. These treatments will be discontinued 3 days prior to the first dose of BGJ398. However, calcium supplements may be restarted as clinically indicated if the subject develops hypocalcemia.

### 4.2.5 Herbal medications

Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

# 5 BIOSPECIMEN COLLECTION

- Sampling time points are detailed in schedule of events section
- The total amount of blood drawn throughout the study will be approximately 584 mL over a period of 9 months. The maximum amount of blood drawn during one study visit will be 143 mL and the maximum amount drawn over an 8-week period will be 265 mL. This amount is less than the NIH guidelines of 10.5 ml/kg/8 weeks (< 550 mL) for adults.

  Drawing blood for the tests and placement of IV catheters may cause discomfort or a bruise at the injection site, and rarely, an infection may occur. Blood drawing by experienced personnel limits the risk of excessive pain, bruising and infection. Twenty-four hour blood sampling is inconvenient to the subject and will cause sleep disruption. Sampling will be done through an indwelling catheter, PICC line, or repeated venipuncture. Indwelling catheterization is associated with a very small risk of infection. No special handling instructions are needed for laboratory tests specified in schedule of events except for FGF23, which will be analyzed in Dr. Collins lab (SOP provided upon request) (Table 5.1).

Table 5.1:

| **Test/assay** | **Volume blood (approx)** | **Type of tube** | **Collection point (+/- 48hrs)** | **Location of specimen analysis** |
|---|---|---|---|---|
| FGF23 | 4 mls | EDTA | Detailed in schedule of events | Building 30/218. Dr. Collins lab. Specimen processing per SOP #17 |

## 5.1 SAMPLE STORAGE, TRACKING AND DISPOSITION

Research samples collected from subjects consented to this protocol will be stored in locked freezers (at -80 C) belonging to the Craniofacial and Skeletal Diseases Branch located in Building 30 on the NIH Bethesda campus. Each research sample will be labeled with the subject ID number, collection date, and specimen type. Study staff will use a computer-based specimen tracking system the NIH NICHD Clinical Trials Database (CTDB) Tracking System accessed via secure NIH servers. The system will be used to document sample collection, notify laboratories of shipments, track shipments, and provide details on the disposition of all samples. If a patient withdraws consent the participants data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved. The principal investigator is responsible for management of samples and data at the completion of the protocol. The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB and the NIDCR Clinical Director. Samples will be destroyed at the end of the protocol unless there has been IRB approval to retain them.

### 5.2 SAMPLES FOR GENETIC/GENOMIC ANALYSIS: NOT APPLICABLE.

**5.2.1 Description of the scope of genetic/genomic analysis: Not Applicable.**

**5.2.2 Description of how privacy and confidentiality of medical information/biological specimens will be maximized: Not applicable.**

**5.2.3 Management of Results: Not Applicable.**

**5.2.4 Genetic counseling: Not Applicable.**

## 6 DATA COLLECTION AND EVALUATION

### 6.1 DATA COLLECTION

All data will be kept secure. Data collected in this study will be integrated into a study specific database using the NIH NICHD Clinical Trials Database (CTDB), a web-based electronic data capture (EDC) system compliant with Part 11 Title21 of the Code of Federal Regulations. Pre-formatted protocol specific electronic case report forms (eCRFs) as part of the database will be developed and approved by the investigational team in collaboration with the NICHD CTDB development team. Study data will be primarily extracted from in-house secured NIH medical record systems including CRIS, BTRIS and medical charts. Lab data collected outside of NIH will be confidentiality faxed to a secured private fax machine in a locked office. Paper source documentation will be kept in a locked office. The investigational staff will complete eCRFs on a rolling basis utilizing data from NIH medical record data systems, outside lab reports and paper source documents. The investigational staff will keep records of files considered source documents, including those from the hospital chart and research chart.

The PI will be responsible for overseeing entry of data into the password protected EDC system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators, research nurses and/or a contracted data manager(s) will assist with the data management efforts. All human subject personally identifiable information (PII) as defined in accordance to the Health Insurance Portability and Accountability Act, eligibility and consent verification will be recorded. Primary data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have coded identifiers so that research data can be attributed to an individual human subject participant.

**End of study procedures:** Data will be stored according to HHS and FDA regulations as applicable.

**Loss or destruction of data:** Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

**Exceptions for data collection/recording on case report forms:**

- Only clinically significant vital sign abnormalities and lab results will be reported as Adverse Events

- Individual lab values for general safety and monitoring will not be recorded in eCRF, unless clinically significant or relate to a protocol specific outcome as listed below. NIH or outside facility lab reports should be referenced results and will serve as source documentation. Date, time and designation of "significance" will be recorded in eCRF for all lab tests recorded. The following individual lab values will be recorded directly on the eCRF:
    - FGF23
    - TRP
    - TmP/GFR

## 6.2 DATA SHARING PLANS

### 6.2.1 Human Data Sharing Plan

For future research collaborations the Principal Investigator will seek NIH IRB review and approval for sending coded data to non-NIH investigator(s). The principal investigator will identify the names of the collaborating researchers and their affiliated institutions, as well as intended plans for use at the time of submission.

The current plan for data sharing is as follows:

**What data will be shared?**

I will share human data generated in this research for future research as follows *(check all that apply)*:

_X_ De-identified data in BTRIS (automatic for activities in the Clinical Center)

_X__ De-identified or identified data with approved outside collaborators under appropriate agreements

**How and where will the data be shared?**

Data will be shared through *(check all that apply):*

_X_ BTRIS (automatic for activities in the Clinical Center)

_X__ Approved outside collaborators under appropriate individual agreements.

_X__ Publication and/or public presentations.

**When will the data be shared?** *(check all that apply)*

**_X__** Before publication.

_X_ At the time of publication or shortly thereafter.

### 6.2.2 Genomic Data Sharing Plan: Not Applicable.

## 6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 4 weeks ± 3 days.

Response and progression will be evaluated by biochemical evaluation (FGF23, mineral panel, 1, 25-$(OH)_2$ levels, alkaline phosphatase, TRP, TmP/GFR) every 2 weeks ± 3 days.

**Definitions**

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with BGJ398.

Evaluable for objective response: The objective response is primarily determined by biochemical changes. All subjects will have, as part of the inclusion criteria, elevated plasma FGF23 and low phosphorous levels. A change in FGF23 and phosphorous levels will be used to evaluate the objective response.

Evaluable Non-Target Disease Response: Not applicable to our protocol as some of our patients have no tumor identified. We evaluate the efficacy of BGJ398 based on biochemical parameters.

### 6.3.1 Disease Parameters

Measurable disease: The disease is measured in terms of biochemical parameters (FGF23, mineral panel, 1, 25-$(OH)_2$-Vitamin D, 25-OH-Vitamin D, alkaline phosphatase, TRP, TmP/GFR every 2 weeks ± 3 days.

Non-measurable disease.: Not applicable.

Target lesions. Not applicable.

Non-target lesions: Not Applicable.

### 6.3.2 Methods for Evaluation of Measurable Disease

All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 1 week ± 4 days before the beginning of the treatment.

The labs done in between NIH visits will be done at the patient's local laboratories; at these local laboratories, only C-terminal FGF23 will be measured as intact FGF23 is not commercially available. Both intact and C-terminal FGF23 levels will be measured by ELISA (Immutopics, Athens, OH and Mayo Medical Laboratories, Rochester, MN) after each NIH visit. We will compare the off-drug levels of FGF23 and blood phosphorous levels with that of baseline levels for evaluating the efficacy of the drug.

### 6.3.3 Response Criteria

#### 6.3.3.1 Evaluation of Target Lesions: Not Applicable.

Complete Response (CR): Not applicable.

Partial Response (PR): Not applicable.

Progressive Disease (PD): Not applicable.

Stable Disease (SD): Not applicable.

#### 6.3.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Normal FGF23 and phosphorous levels off drug are considered as complete metabolic response (CR).

Non-CR/Non-PD: Off drug decrease in FGF23 levels by 50% but still greater than the upper limit of the normal range and increase in plasma phosphorous levels by 50% but not to the normal range is considered as partial metabolic response.

Progressive Disease (PD): Increase in FGF23 levels, and decreased phosphorous levels (compared to that of baseline), off the drug is considered a progressive disease.

#### 6.3.3.3 Evaluation of Best Overall Response

Best overall response is determined in terms of FGF23 levels and blood phosphorous levels at the end of 9 months (6 months on drug and 3 months off the drug).

Complete Response (CR): Normal FGF23 and phosphorous levels are considered as complete metabolic response (CR).

Non-CR/Non-PD: Off drug decrease in FGF23 levels by 50% but still greater than the upper limit of the normal range and increase in plasma phosphorous levels by 50% but not to the normal range is considered as partial metabolic response.

Progressive Disease (PD): Increase in FGF23 levels, and decreased phosphorous levels (compared to that of baseline), off the drug is considered a progressive disease.

### 6.3.4 Duration of Response

Duration of overall response: If complete metabolic response is achieved at the end of the 1 week end-of-study pharmacodynamic period (see section 3.4) following 24 weeks of BGJ398, the subjects will be followed for an additional 11 weeks (± 2 weeks). If the subject has not had complete metabolic response at the end the 1 week end-of-study pharmacodynamic period or at any time during the follow-up, he/she will be offered the option of entering the extension phase or referred for alternative treatments.

### 6.3.5 Progression-Free Survival: Not Applicable.

### 6.3.6 Response Review: Not applicable.

## 6.4 TOXICITY CRITERIA

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

# 7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING

## 7.1 DEFINITIONS

### Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections **7.2, 7.4, 7.5.**

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

### Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

### Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

### Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

**Serious Adverse Event**

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

**Disability**

A substantial disruption of a person's ability to conduct normal life functions.

**Life-threatening adverse drug experience**

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

**Protocol Deviation**

Any change, divergence, or departure from the IRB-approved research protocol.

**Non-compliance**

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

**Unanticipated Problem**

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**

- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

## 7.2 NCI-IRB REPORTING

### 7.2.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

### 7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI or designee will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

Principal Investigator or designee will use the summary table 7.2.2 to report of adverse events that have occurred on the protocol since the previous continuing review and in aggregate.
Table 7.2.2: Summary table of adverse events:

| System Organ Class | CTCAE Term | Grade | # of Events since last CR | Total # of Events | Attribution to Research | Serious? | Unexpected? |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

### 7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will be reported to the NCI IRB.

## 7.3 NCI GUIDANCE FOR REPORTING EXPEDITED ADVERSE EVENTS FOR MULTI-CENTER TRIALS: NOT APPLICABLE

## 7.4 IND SPONSOR REPORTING CRITERIA: NOT APPLICABLE

## 7.5 FDA REPORTING CRITERIA

### 7.5.1 IND Safety Reports to the FDA

The Sponsor will notify the FDA of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible but no later than 7 calendar days of initial receipt of the information using the MedWatch Form 3500a.

The Sponsor is also responsible for reporting any:

- suspected adverse reaction that is both serious and unexpected
- any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

to the FDA no later than 15 calendar days after determining that the information qualifies for reporting using the MedWatch Form 3500a. If FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendars days after receiving the request.

### 7.5.2 FDA Annual Reports

Principal Investigator will submit a brief report annually of the progress of the trial within 60 days of the anniversary date that the IND went into effect as indicated in 21CFR 312.33, and any associated FDA correspondences regarding the IND annual report.

### 7.5.3 Expedited Adverse Event Reporting Criteria to the IND Manufacturer

### 7.5.4 Reporting responsibility

Each serious adverse event must be reported by the investigator to QED within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported to QED within 24 hours of receiving it. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to study drug (or therapy), the Medical Safety Expert of the Drug Safety & Epidemiology (DS&E) Department may contact the investigator to obtain further information. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug (or therapy) that this serious adverse event has been reported.

### 7.5.5 Reporting procedures

The investigator must complete the FDA MedWatch 3500a form and QED SAE report form in English, assess the relationship to study treatment and send the initial completed MedWatch form and QED SAE Report Form to Chiltern Pharmacovigilance via fax or email within 24 hours of becoming aware of the SAE. The original FDA MedWatch form and QED SAE report form must be kept with the case report forms at the study site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The MedWatch form and QED SAE report form must be retained. Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety Within 24 hours of the site becoming aware of a pregnancy in either a study subject or the partner of a study subject, the Investigator is required to notify QED by completing the Pregnancy Notification Report and sending to Chiltern Pharmacovigilance via email (or) fax. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications using the Pregnancy Follow-up Report form.

## 7.6 NIH OFFICE OF BIOTECHNOLOGY ACTIVITIES (OBA)/INSTITUTIONAL BIOSAFETY COMMITTEE (IBC) REPORTING CRITERIA: NOT APPLICABLE

## 7.7 DATA AND SAFETY MONITORING PLAN

### 7.7.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis, generally weekly, when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator or designee will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

### 7.7.2 Sponsor Monitoring Plan

This trial will be monitored by Clinical Research Associates (CRAs) employed by Rho, Inc on contract with NIDCR DIR, NIH. The CRA's are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct. Clinical monitoring for this study will be guided by a Clinical Monitoring Plan that is developed jointly by the PI, OCTOM, the NIDCR Clinical Director and Rho.

The purpose of clinical monitoring is to ensure the rights of human subjects are protected, the study is implemented in accordance with the protocol, and the integrity of study data is maintained.

The monitoring plan will provide details about the monitoring activities including the frequency, procedures, and level of monitoring activities. Monitoring activities will include a study initiation visit, interim site monitoring visits, close out visit and, if necessary, for cause visits. Some monitoring activities may be performed remotely (e.g., review of regulatory documents), while others will take place on site (e.g., verification of study database entries against source documentation).

The frequency of interim monitoring visits will be based on patient accrual. Routine monitoring visits may be difficult to schedule on a regular basis due to unknown timing of patient accrual. A monitoring visit schedule, based on enrollment frequency, will be developed with the CRO and site staff in order to maximize oversight and minimize inconvenience to the site staff. If subjects can be scheduled in close time proximity, multiple subjects will be monitored at one visit.

### 7.7.3 Safety Monitoring Committee (SMC): Not Applicable

### 7.7.4 Data Safety Monitoring Board (DSMB)

The NIDCR Data and Safety Monitoring Committee (DSMC) will have oversight responsibilities for the study. The committee will include members with expertise in a broad range of areas, including human subject protection, research ethics, clinical trial implementation, biostatistics, and medical bone and mineral metabolism. In addition to any safety alerts, the DSMC will review data approximately twice a year related to enrollment progress, trial implementation, subject safety, and clinical efficacy. The DSMC will also consider current information from other sources on the biology of the disease, the investigational product, and the patient population under study. Based on these reviews, the DSMC will make recommendations to the principal investigator and the NIDCR clinical director concerning the continuation, modification, or termination of the trial. The roles and responsibilities of committee members and meeting procedures will be formally described in a charter.

The DSMC and the investigator will review the annual DSMC reports to determine whether the aggregate safety data should be reported to the FDA in an expedited manner.

Aggregate data will be reported in an expedited manner to the FDA if the DSMC or the investigator believes those data represent an unexpected set of related SAEs for which there is a reasonable possibility that they were caused by the study drug.

## 8 STATISTICAL CONSIDERATIONS

### 8.1 STUDY POPULATIONS

The safety and intent-to-treat populations are defined as all patients who received at least one dose of study drug.

The per protocol population is define as the group of patients who complete the protocol without any major protocol deviations and have received 65% of study drug per cycle.

### 8.2 RACIAL, ETHNIC, AND GENDER MAKE-UP OF THE STUDY POPULATION

Due to this limited pool of available TIO patients and an expected sample size of only 10 patients, all eligible patients will be enrolled without regard for their race, ethnicity, or gender. A listing of each patient's race, ethnicity, and gender will be reported. No sub-analyses or stratifications based upon race, ethnicity, gender, or other parameters are planned due to the small expected sample size.

### 8.3 STATISTICAL ANALYSIS OF THE PRIMARY OBJECTIVE AND ENDPOINT

The primary objective is to induce a complete metabolic response in subjects with tumor-induced osteomalacia (TIO) with BGJ-398. The primary endpoint, complete metabolic response, is defined as the percent of patients in the ITT Population achieving both normal FGF23 and phosphorus levels in the blood at the end of the 12-week follow-up period. The complete response rate will be reported with its exact 95% confidence limits. Patients that for any reason are missing their response status will be counted as failures with respect to achieving complete response.

### 8.4 STATISTICAL ANALYSIS OF THE SECONDARY ENDPOINTS

Secondary study endpoints will include:

- Complete metabolic response rate at the bi-weekly visits.
- Combined complete and partial metabolic response rate: partial response defined as both a decrease of at least 50% in FGF23 and an increase of at least 50% in phosphorus in the plasma at the bi-weekly, and 12-week follow-up visits.
- Biochemical measures of disease including plasma concentrations of FGF23, mineral panel, 1,25-$(OH)_2$-Vitamin D, alkaline phosphatase, tubular reabsorption of phosphate, TRP, and TmP/GFR measured every 2 weeks.
- Eight quality of life domains from the RAND SF-36 survey measured at baseline and every 4 weeks.
- PROMIS survey measured at baseline and every 4 weeks
- Strength testing measured at baseline and every 4 weeks
- Six-minute walk test assessed at baseline, 24 weeks and 36 weeks.
- Radiographic evidence of TIO (in subjects with measurable tumor burden).

All analyses on the secondary endpoints will be performed on both the intent-to-treat and the per protocol populations.

Similar to the primary analysis, the complete response rate will be estimated with its exact 95% confidence limits, but at each bi-weekly sampling visit. The combined complete and partial response rate will be summarized as percent with its exact 95% confidence limits at every bi-weekly visit but with the 12-week follow-up visit rate of primary interest. Patients that for any

reason are missing their response status will be counted as failures with respect to achieving complete or partial response.

The biochemical measure of disease secondary endpoints will be analyzed using repeated measures mixed models with the contrast of primary interest between the baseline and the 12-week follow-up visit. Additional post hoc comparisons with corrections for multiple comparisons will compare the measures at the end of each cycle to baseline. Of primary interest will be the reduction of FGF23 concentrations, the increase in both plasma phosphorus and 1,25-$OH_2$-vitamin D, and the other biochemical parameters. These concentration endpoints will be log-transformed if appropriate. The muscle-strength testing, SF-36, and PROMIS will also be analyzed using repeated measures mixed models similarly to the biochemical measures of disease. Patients without baseline values for a particular biochemical measure will be excluded from the analysis. Missing values other than baseline measures will be adjusted-for within the repeated measures, mixed model using restricted maximum likelihood techniques.

Radiographic evidence of TIO will be summarized in patient listings.

### 8.5 SAMPLE SIZE JUSTIFICATION

The sample size of 10 is based upon the highest enrollment that can be reasonably expected. Tumor-induced osteomalacia (TIO) is a very rare neoplastic syndrome; it is expected that only 10 patients will be found within the recruitment period and population that are eligible for enrollment.

The primary study endpoint is the complete metabolic response rate with its 95% confidence limit (95% CL). Patients withdrawing for any reason any time after receiving their first dose of study drug will remain in the ITT population and be counted as a treatment failure. Table 8.4 lists the resulting exact 95% CL for each of the possible response rates for sample sizes of 9 and 10. It is hypothesized that BGJ398 will be effective therapy in 40-60% of the subjects, based on the previous observation that 40-60% of TIO tumors harbor the fibronectin-fibroblast growth factor receptor-1 (FN1/FGFR1) fusion gene. A 60% complete response rate at N=10 would result in a lower 95% confidence bound of 26%. A lower 50% complete response rate at N=10 would still give a lower 95% confidence bound of 18.7% for the complete response rate. Finally, if the target population could not be reached with the final sample size being just 9 and with only 5 of 9 patients having a complete response (55.5%), the lower bound of the 95% CL for the complete response rate would be 21.1%. All three of these lower 95% CL boundaries of the complete response rates: 18.7, 21.1, and 26.2%, could justify BGJ398 therapy for patients with TIO depending on the risks relating to toxicity.

Table 8.4. Listing of the exact 95% confidence limits that would be obtained for each possible complete response rate with study's sample sizes of 9 and 10. The exact 95% confidence limits are based upon the binomial distribution.

| **Sample Size N=10** | | **Sample size N=9** | |
|---|---|---|---|
| **Complete Response Rate (%)** | **Exact 95% CL* (%)** | **Complete Response Rate (%)** | **Exact 95% CL* (%)** |
| 0 | (0.00, 30.8) | 0.0 | (0.00, 33.6) |
| 10 | (0.25, 44.5) | 11.1 | (0.28, 48.3) |
| 20 | (2.5, 55.6) | 22.2 | (2.8, 60.0) |

| | | | |
|---|---|---|---|
| 30 | (6.7, 65.3) | 33.3 | (7.5, 70.1) |
| 40 | (12.2, 73.8) | 44.4 | (13.7, 78.8) |
| 50 | (18.7, 81.3) | 55.6 | (21.1, 86.3) |
| 60 | (26.2, 87.8) | 66.7 | (29.9, 92.5) |
| 70 | (34.8, 93.3) | 77.8 | (40.0, 97.2) |
| 80 | (44.4, 97.5) | 88.9 | (51.8, 99.7) |
| 90 | (55.5, 99.8) | 100.0 | (66.4, 100.0) |
| 100 | (69.2, 100.0) | | |

# 9 COLLABORATIVE AGREEMENTS (IF APPLICABLE)

## 9.1 AGREEMENT TYPE

A Materials Cooperative Research and Development Agreement (mCRADA) has been established with QED to provide funding and study drug for this investigator-initiated study. De-identified coded samples will be sent to QED or their designated agent for pharmacokinetic analysis. De-identified samples will not be sent to other non-NIH collaborators unless an MTA has been executed.

## 9.2 MULTI-INSTITUTIONAL GUIDELINES

This is a single site study.

### 9.2.1 IRB Approvals: Not Applicable.

### 9.2.2 Amendments and Consents: Not Applicable.

# 10 HUMAN SUBJECTS PROTECTIONS

## 10.1 RATIONALE FOR SUBJECT SELECTION

Selection of subjects will not be limited by gender, race, ethnicity or language. Men and women over age 85 have been excluded, as there are no safety data for this age group. Cognitively impaired subjects are also excluded from the study as early recognition and communication of side effects is essential to avoid toxicity.

## 10.2 PARTICIPATION OF CHILDREN

Children are excluded from the study, as there are no safety data for people age < 18 years in phase 1 trials of BGJ398 to date.

## 10.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **10.4**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated

or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team(ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 and NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

## 10.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

It is anticipated that participants in this study will benefit directly from their treatments with conventional therapy and may benefit from therapy with the investigational drug.

### 10.4.1 CLASSIFICATION OF RISK

This study is classified as research involving more than minimal risk. This risk is justified as the current treatment is inadequate and associated with morbidity.

Risks of the study are reasonable in relation to the anticipated benefit.

**Risks/Benefits Analysis**

As discussed in section 1.2, medical treatment of patients whose tumors cannot be located, or are inoperable or widely metastatic, is difficult. It involves at least thrice daily phosphate, which is poorly tolerated due to diarrhea and can lead to secondary/tertiary hyperparathyroidism, and active vitamin D, which can result in iatrogenic nephrocalcinosis/nephrolithiasis.

## 10.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

### 10.5.1 Designation of Those Obtaining Consent

Informed consent will be obtained by the principal investigator or an associate investigator.

### 10.5.2 Consent Procedures

All subjects (or their legally authorized representative) will be required to sign and date a consent form before participating in any portion of the study. All participants will receive a verbal explanation in terms used to their comprehension of the purposes, procedures, and potential risks of the study and their rights as research participants. Participants will also have the opportunity to carefully review the written consent form and ask questions regarding this study prior to signing. A copy of the informed consent will be given to the prospective subject for review, and the principal investigator or an associate investigator, will review the consent form with the subject. In the presence of a witness, the investigator will request the subject's signature, indicating consent. The subject will be informed that participation is voluntary and that he/she may withdraw from the study at any time, for any reason. If the subject is non-English speaking, a consent will be obtained in the presence of an interpreter.

### 10.5.3 Consent Documents

The consent document captures all required elements, including the purposes, procedures, benefits, and potential risks of the study. The consent process will be documented in the subjects' medical records. The documentation of the consent process will include the following elements:

- ✓ Date and time of consent
- ✓ Topics discussed with the subject (e.g. risk, benefits, alternatives)
- ✓ Confirmation that subject had adequate time to review the consent, that the subject's questions were answered, and that a copy of the consent was provided to the subject

The consent forms will be updated or revised whenever important new safety information is available, whenever the protocol is amended, or whenever any new information becomes available that may affect participation in the study. The original forms will become part of the permanent medical record and copies will be provided to the subjects.

## 11 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

### 11.1 DRUG BGJ398

### 11.1.1 Source

The BGJ398 capsules used in this study will be supplied under a collaborative agreement with the manufacturer, QED.

### 11.1.2 Toxicity

BGJ398 showed no evidence of in vitro genotoxicity in Ames and chromosome aberration tests and no evidence of phototoxicity in a 3T3 photo-cytotoxicity test. In vitro safety pharmacology assessment of BGJ398 revealed a decrease in human Ether-à-go-go-related gene (hERG) channel activity with an IC50 of 2.0 μM (1121ng/ml).

In vivo safety pharmacology studies in rats and dogs did not reveal any effects on central nervous or respiratory systems and on hemodynamic or electrocardiographic parameters, respectively.

In repeated dose (oral gavage; up to 4-weeks) toxicity studies, BGJ398 did lead to increases in blood FGF23 and blood phosphorous associated with partially reversible ectopic mineralization (kidney, lung, vascular and digestive systems) along with largely reversible changes in renal function parameters and bone growth plate thickening / retention of the primary spongiosa in rats (≥ 10 mg/kg/day) and dogs (≥ 10 mg/kg/day). These effects were deemed to be on-target effects mediated by pharmacological inhibition of FGFR.

In rats, corneal changes were found upon 4 weeks of BGJ398 treatment consisting of irreversible, slight corneal opacity in dose-dependent incidence, as assessed by in vivo ophthalmology, associated with reversible, diffuse epithelial keratopathy at the highest dose of 10 mg/kg. In the 4-week GLP oral toxicity study in rats, the severely toxic dose in 10% (STD10) was considered to

be at 10 mg/kg/day which resulted in premature death in one (1/30) animal. Doses of 20 mg/kg/day in rats did lead to vasculopathy associated with moribundity after 6 administrations.

In dogs, the highest non-severely toxic dose (HNSTD) was considered to be at 10 mg/kg/day leading to minimal, fully reversible retention of the primary spongiosa and minimal increase in mineralization in lung and kidney without observed functional impairment were observed.

As of data cut-off date September 6, 2016 207 patients have received at least one dose of BGJ398. Forty-three patients were enrolled to dose escalation cohorts and 164 patients to dose expansion arms.

Enrollment to the dose escalation cohorts was as follows: 5mg [N=3], 10mg [N=3], 20mg [N=4], 40mg [N=6], 60mg [N=3], 100mg [N=6], 50 mg bid [N=4], 125mg [N=8], and 150mg [N=6]. MTD was identified to be 125 mg qd on a continuous dosing schedule.

Dose expansion consists of 4 arms enrolling different patient populations on two different dosing schedules at 125 mg (daily or 3 weeks on/1 week off in 28-day cycles). Arm 1 [N=28] enrolled FGFR1-amplified advanced or metastatic squamous NSCLC with FGFR1 amplification on the continuous dosing schedule. Arm 2 [N=21] enrolled advanced solid malignancies with any FGFR mutation or amplification dosed continuously. Arm 3 [N=49] enrolled advanced solid malignancies with any FGFR genetic alteration, mutation, or amplification on the 3 weeks on/1 week off dosing schedule. Arm 4 [N=66] enrolled advanced or metastatic urothelial cell carcinoma (UCC) with FGFR3 mutation or gene fusion on the 3 weeks on/1 week off dosing schedule.

The 3 weeks on/1 week off schedule was implemented based on observations of the timing and duration of drug interruptions during Cycle 1 necessitated by episodes of hyperphosphatemia. The data indicated that the median time to drug interruption was 22 days and the median duration of the interruption was 7 days.

At the time of data cutoff, 21 patients were still receiving study medication. Of the 186 patients who have discontinued from the study, 135 discontinued treatment due to progression of disease, 28 discontinued due to adverse events, 6 died while on study, 15 discontinued due to withdrawal of consent, 1 due to administrative problems, and 1 due to protocol deviation.

Ocular adverse events (regardless of BGJ398 relationship) occurred in 47.3 % of patients. Most of the eye disorders occurred at doses ≥ 100 mg administered daily or on the 3 weeks on/1 week off dosing schedule, and were mild to moderate in severity (grade 1 or 2). The most frequent (17.4 %) included blurred vision (7.2%), and keratitis (6.3%). Grade 1 or 2 retinal events (8.7%) included retinopathy, retinal detachment, sub-retinal fluid, retinal edema and retinal hemorrhage. One patient had a grade 3 retinal detachment. Grade 1 cornea events (3.9%) consisted of corneal toxicity, corneal disorder, corneal scar, corneal deposits, corneal erosion, corneal abrasion and epitheliopathy. A grade 2 event, corneal thickening, occurred in 1 patient (corneal thickening). Keratopathy occurred in 1.4% and punctate keratitis occurred in 2.4 % patients.

Medically significant ocular AE's (events that were grade 3, n=4; events reported

as a DLT, n=1; or events causing study discontinuation, n=8) occurred in 11 patients. Of the 28 patients with AE's leading to discontinuation, an eye disorder was the reason in 8 patients. Approximately half of the eye -related events resolved prior to end of study, however, continuing follow up after the end of study visit was not consistently performed to confirm eventual resolution of events ongoing at study discontinuation.

Other treatment emergent AE's (regardless of BGJ398 relationship) reported in > 20% include: increases in phosphorus levels (hyperphosphatemia, 57.5%, and blood phosphorus increased, 9.2%), constipation (39.6%), decreased appetite (36.2%), fatigue (34.3%), stomatitis (33.3%), nausea (31.4%), blood creatinine increased (28.5%), diarrhea (27.5%), alopecia (26.1%), dry mouth (23.7%), vomiting (20.8%), and anemia (20.3%).

Approximately 58% of patients experienced at least one grade 3 or 4 event regardless of the relationship to BGJ398. In addition to medically significant ocular AE's listed above, Grade 3 or 4 events that occurred in at least 5% of patients included increased lipase (6.8%) and alanine aminotransferase (5.3%). Overall, most adverse events reported have been mild to moderate in severity, reversible, and unrelated to BGJ398.

Four DLTs occurred in four patients enrolled in the dose escalation part of the study. The MTD as determined by DLT was based on the following events:

- One grade 3 event of AST/ALT elevation was reported in the 100mg cohort.
- One patient enrolled to the 125 mg cohort experienced hyperphosphatemia for greater than 14 days despite adequate therapy that resulted in study drug interruption.
- Two patients enrolled to the 150 mg cohort experienced DLTs. One patient experienced grade 1 corneal toxicity. The second patient experienced grade 3 AST/ALT elevations, which led to study treatment interruption and dose reduction.

### 11.1.3 Formulation and preparation

BGJ398 will be supplied in Size 00 hard gelatin capsules. Each capsule will contain either 25 mg (pink opaque or pink opaque/yellow opaque capsules) or 100 mg (pink opaque or yellow opaque capsules) of BGJ398 free base (white to greyish powder). BGJ398 capsules are stored in white HDPE bottles with 28 capsules per bottle.

The capsule fills are composed of the BGJ398 free base and other commonly used excipients for solid oral dosage forms. The common excipients in all formulations include microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide. Other excipients such as mannitol, lactose monohydrate, polyvinylpolypyrrolidone, hypromellose and croscarmellose sodium may be used as the formulation evolves during development.

### 11.1.4 Stability and Storage

All study drugs must be received by a designated member within the NIH Clinical Center Department of Pharmacy, and kept in a secured location under appropriate storage conditions.

BGJ398 capsules are stable under refrigerated condition between 2ºC-8ºC. BGJ398 are found to be stable between the temperatures of -20ºC to +2°C for a maximum of 14 consecutive days or in room temperature between +8ºC to +25ºC for a maximum of 3 consecutive days.

### 11.1.5 Administration procedures

Patients will be provided with adequate supply of BGJ398 for self-administration at home until at least their next scheduled study visit.

The following general guidelines should be followed for BGJ398 administration:

- Patients should be instructed to take the daily dose of BGJ398 in the morning, at approximately the same time each day (24 ± 2 hr interval).
- BGJ398 should be administered in the fasted state, at least 1 hour before or 2 hours after a meal.
- BGJ398 should be taken with a large glass of water (~250 mL) and consumed over as short a time as possible. Patients should be instructed to swallow the correct number of 25 mg or 100 mg capsules comprising the appropriate dose whole and not chewed, crushed, dissolved or divided.
- If the patient forgets to take the scheduled dose in the morning, he/she should not take the dose more than 2 hours after the usual time and should continue treatment the next day. Any doses that are missed should be skipped altogether and should not be replaced or made up at the next scheduled dosing.
- If vomiting occurs following the dosing of study drug, re-dosing is not permitted that same day. Dosing should resume the next day. This event needs to be noted appropriately.
- BGJ398 is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of both compounds, and limit bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. Therefore, BGJ398 should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.
- Patients must avoid consuming Seville (blood) oranges or juice, grapefruit, grapefruit juice, grapefruit hybrids, or pomelos from 7 days prior to the first dose of study medication through the end of study participation. This is due to a potential CYP3A4 interaction with study medication. Normal oranges and orange juice are allowed.

Subjects will be instructed to return the unused study medication to the NIH at each visit.

BGJ398 will be dispensed in accordance with this protocol. The NIH Clinical Center Department of Pharmacy and the investigator are responsible for keeping accurate records of the amount dispensed to and returned by the patients and the amount remaining at the conclusion of the study.

### 11.1.6 Incompatibilities

BGJ398 is an orally bio-available, selective and ATP competitive pan-fibroblast growth factor receptor (FGFR) kinase inhibitor which has demonstrated anti-tumor activity in preclinical, in vitro and in-vivo tumor models harboring FGFR genetic alterations. BGJ398 belongs to the pyrimidinyl

aryl urea chemical class and its chemical name is 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-{6-[4-(4-ethyl-1-piperazin-1-yl)phenylamino]-pyrimidinyl-4-yl}-1-methylurea phosphate(1:1).

A copy of drug brochure will be provided to the pharmacy department. Please refer to section 4 for concomitant therapy/drug interactions and section 11.1.2 for potential toxicities.

### 11.2 DISCONTINUATION OF THE STUDY

QED reserves the right to discontinue support for any study under the conditions specified in the clinical trial agreement.

## 12 CHANGES TO THE PROTOCOL

Any change or addition to this protocol requires a written protocol amendment that must be approved by QED and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB. A copy of the written approval of the IRB/IEC/REB, must be sent to QED.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes.

## 13 PUBLICATION OF RESULTS

Any formal presentation or publication of data from this trial may be published after review and comment by QED and prior to any outside submission. QED must receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge QED' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of QED and, in accord with the trial contract and shall not permit disclosure of QED confidential or proprietary information.

## 14 DISCLOSURE AND CONFIDENTIALITY

The investigator agrees to keep all information provided by QED in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by QED (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by QED to the investigator may not be disclosed to others without direct written authorization from QED, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

## 15 DECLARATION OF HELSINKI

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

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Appendices:

Appendix 1: RAND SF-36

Appendix 2: PROMIS

Appendix 3: Patient Instructions