PROTOCOL

TITLE:	**A PHASE II, RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF BFKB8488A COMPARED WITH PLACEBO IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS**
PROTOCOL NUMBER:	GC41033
VERSION NUMBER:	6
EUDRACT NUMBER:	2019-001897-27
IND NUMBER:	[redacted]
NCT NUMBER	NCT04171765
TEST PRODUCT:	BFKB8488A (RO7040551)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 3 June 2019
DATES AMENDED:	Version 2: 23 August 2019 Version 3: 9 March 2020 Version 4: 6 May 2020 Version 5: 28 October 2020 Version 6: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
10-May-2021 21:47:21	Company Signatory	[redacted]

PROTOCOL HISTORY

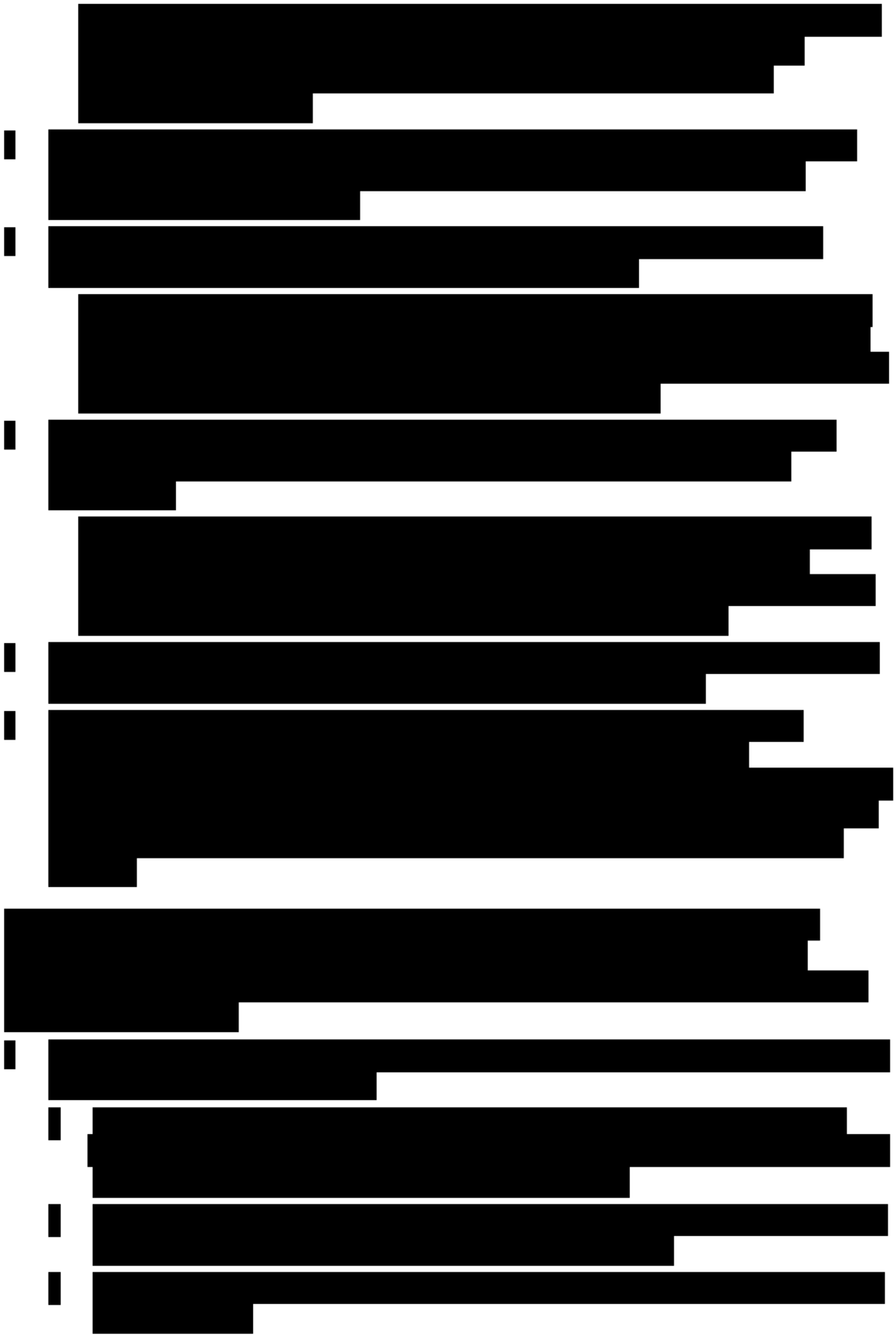
Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
6	See electronic date stamp on title page	---	---	---
5	28 October 2020	United Kingdom	1	12-Jan-2021
4	6 May 2020	---	---	---
3	9 March 2020	---	---	---
2	23 August 2019	---	---	---
1	3 June 2019	---	---	---

PROTOCOL AMENDMENT, VERSION 6: RATIONALE

[redacted]

[redacted]

[redacted]



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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF BFKB8488A COMPARED WITH PLACEBO IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS**
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NCT NUMBER	NCT04171765
TEST PRODUCT:	BFKB8488A (RO7040551)
PHASE:	Phase II
INDICATION:	Non-alcoholic steatohepatitis
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of BFKB8488A compared with placebo in patients with non-alcoholic steatohepatitis (NASH). Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of BFKB8488A compared with placebo on the basis of the following endpoint:

- Proportion of patients with resolution of NASH on overall histopathological reading, without worsening of fibrosis at Week 52. Resolution of NASH is defined as a NAS of 0–1 for inflammation, 0 for ballooning, and any value for steatosis as determined by a central reader. Worsening of fibrosis is defined as any increase in NASH Clinical Research Network (CRN) fibrosis stage as determined by a central reader.

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of BFKB8488A compared with placebo on the basis of the following endpoints:

- Change from baseline in hepatic fat fraction as assessed by magnetic resonance imaging–derived proton density fat fraction (MRI-PDFF) at Week 52
- Proportion of patients with improvement in liver histology from baseline, defined as $\geq$2 points reduction in NAS with at least a 1-point reduction in either lobular inflammation or hepatocellular ballooning AND no worsening of fibrosis stage as determined by a central reader at Week 52
- Proportion of patients with improvement in liver fibrosis greater than or equal to one stage (as defined by the NASH CRN fibrosis stage) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis), determined by a central reader at Week 52

Safety Objective

The safety objective for this study is to evaluate the safety of BFKB8488A compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grading scale
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to evaluate the BFKB8488A PK profile on the basis of the following endpoint:

- Serum concentration of BFKB8488A at specified timepoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to BFKB8488A on the basis of the following endpoint:

- Incidence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, exploratory biomarker, or PK endpoints

Biomarker Objectives

The exploratory biomarker objectives for this study are the following:

- To identify biomarkers that are predictive of response to BFKB8488A (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of BFKB8488A activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:
  - Relationship between MRI-derived biomarkers, adipokines, triglycerides, lipids, liver enzymes, pro-C3, and other biomarkers in blood and tissue samples and efficacy, safety, and PK
- To predict or evaluate histologic changes in response to BFKB8488A on the basis of the following endpoint:
  - Automated image analysis of H&E and trichrome-stained liver biopsies

Health Status Utility Objective

The exploratory health status utility objective for this study is to assess the patient perspective on response to BFKB8488A on the basis of the following endpoint:

- Change from baseline in Appetite Sensations Visual Analogue Scale (VAS) scores at specified timepoints

Study Design

Description of Study

This is a Phase II, randomized, parallel-group, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and pharmacokinetics of BFKB8488A compared with placebo in patients with NASH. [redacted] as determined by the Sponsor's Internal Monitoring Committee [IMC] will be enrolled at multiple investigational sites across the globe. Patients will be randomly assigned to receive either BFKB8488A or placebo *in the fixed dosing cohort* [redacted]

[redacted] In the fixed dose arms, patients will be randomly assigned to receive BFKB8488A 50 mg, BFKB8488A 75 mg, BFKB8488A 100 mg, or placebo. [redacted] Randomized patients will be stratified by diabetes status and fibrosis stage (F1 vs. F2/F3). A maximum of up to approximately 20% of patients with F1 will be enrolled in this study.

The study will consist of a screening period (up to 8 weeks; including an initial screening and a main screening), a subsequent 52-week treatment period, and a 6-week safety follow-up period. The total duration of the study for each patient will be approximately 66 weeks.

During screening (up to 8 weeks), eligibility screening assessments should be completed as early as possible. All eligibility assessments must be completed within the 8-week screening period with the exception of delays in laboratory (including biopsy) and MRI reporting or due to unforeseen scheduling issues. All eligibility assessments should be completed prior to randomization.

Patients will be required to undergo a liver biopsy prior to randomization in order to confirm diagnosis of NASH. An archival liver sample collected within 6 months prior to randomization may be used provided it meets eligibility requirements; otherwise, a fresh biopsy will be taken during the screening period.

To ensure an accurate baseline, two measurements will be taken for AST and ALT for all patients, first during the initial screening and then during the main screening approximately 4 weeks later (at least 2 weeks apart). A Fibroscan® assessment will also be performed during the initial screening to establish a baseline for all patients; [redacted] The initial screening and the main screening may overlap; assessments for the initial screening and main screening may be done at the same time.

If a patient does not meet all eligibility criteria within the screening period *(with up to 2 week allowance for delays in laboratory (including biopsy) and MRI reporting or unforeseen scheduling issues*), re-screening is permitted once, at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 8 weeks after previously signing the consent form. The investigator will record reasons for screen failure in the screening log. Re-screening patients must meet all eligibility criteria. Labs and tests performed within the last 8 weeks prior to re-screening do not need to be repeated (except pregnancy tests, insulin, lipids, AST/ALT, and HbA1c, unless approved by the Medical Monitor). [redacted] The MRI will not need to be repeated if an MRI was performed within [redacted] prior to *randomization*. The biopsy will not need to be repeated if an archival sample is available from a biopsy performed no more than 6 months before randomization. [redacted]

In order to establish a stable baseline for the study, all patients must be compliant with current medication and avoid any atypical physical activity for the week immediately prior to randomization. In addition, patients will be instructed to adhere to a diet consistent with guidelines for weight maintenance and a healthy lifestyle. These instructions should be given to the patients as early as possible during the screening period.

During the treatment period, patients will receive Q2W SC injections of BFKB8488A or placebo. Patients will receive a total of 26 (Q2W) doses.

Patients who complete the treatment period or discontinue treatment early will enter a follow-up period for a total of 6 weeks. Patients will be asked to come in for follow-up and evaluation as described in the schedule of activities.

[redacted]

Internal Monitoring Committee

The incidence and nature of any adverse events, serious adverse events, and laboratory abnormalities will be assessed on an ongoing basis by the Sponsor's IMC. This committee will not be blinded to treatment assignments, and will include a medical monitor, drug safety scientist, and biostatistician from the Sponsor. The PI, site investigators, and site personnel will remain blinded until the completion of the study, except in circumstances where unblinding is determined by the investigator or by the IMC to be important for the safety of a patient. The IMC may request that additional Sponsor scientists (e.g., PK or clinical scientists) participate in data analysis either blinded or unblinded. Members of the IMC will be independent of the operational team responsible for executing the study.

The IMC will review cumulative unblinded safety data at regular intervals during the study. In addition, the IMC will conduct the interim analysis of the efficacy data as needed. Ad hoc meetings may be called in addition to scheduled meetings to help evaluate, and provide recommendations for management of, any emerging potential safety signals. During periodic blinded safety analyses, events that would trigger an ad hoc IMC meeting and review of unblinded data to decide the safety of continuing the study include, but are not limited to, the following:

- Three patients develop the same Grade 3 CTCAE attributed to study drug OR
- Two patients develop any Grade 4 CTCAE attributed to study drug OR
- One patient develops a Grade 5 CTCAE

After reviewing the data, the IMC may make recommendations such as the following:

- The study will continue as planned
- The study will continue with a change in dose level [redacted] or frequency within a treatment arm

  In cases where a dose level or frequency is changed during the study, the IMC may recommend that the study team consider adding up to 30 additional patients to the study, in order to ensure that an adequate number of patients receive the changed dose for an adequate duration.
- [redacted]
- The study will continue with discontinuation of enrollment in a treatment arm
- The study will stop for unfavorable benefit-risk
- Additional analyses will need to be performed
- Enrollment will be held pending further safety evaluation

Specific operational details such as committee composition, frequency and timing of meeting, and member roles and responsibility of the IMC will be detailed in a separate IMC charter.

Target Population

Inclusion Criteria

- Signed Informed Consent Form

- AST ≥ 20
- FibroScan® fibrosis result ≥ *7.0* kilopascals (kPa)
- FibroScan® controlled attenuation parameter (CAP) ≥ *285* decibels per meter (dB/m)

Patients must meet the following criteria during the main screening for study entry:

- Age ≥ 18 and ≤ 75 years at time of signing Informed Consent Form
- Ability to comply with the study protocol (including ability to safely obtain a liver biopsy if needed), in the investigator's judgment
- Hepatic steatosis on MRI (≥ 8% average liver PDFF) prior to randomization
- Confirmed diagnosis of NASH as documented through central testing of a representative liver sample performed no more than 6 months before randomization, with a NAS greater than or equal to 4 with at least 1 point each in inflammation and ballooning along with a NASH CRN fibrosis score between F1 and F3 (a maximum of approximately 20% of patients with F1 will be enrolled). The biopsy must be performed while the patient is not on any treatment prescribed for the purpose of this study or on any investigational therapy for the treatment of NASH.

  If an archival liver sample is unavailable or does not meet eligibility criteria, liver tissue must be obtained from a biopsy performed at screening.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use a contraceptive method with a failure rate of < 1% per year during the treatment period and for at least 42 days after the final dose of study drug. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 132 days after the final dose of study drug. Men must refrain from donating sperm during this same period.

With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for the duration of the pregnancy to avoid exposing the embryo.

- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Inability to undergo an MRI for any reason (such as metal implants or devices, claustrophobia, and/or patient size
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 42 days after the final dose of BFKB8488A

  Women of childbearing potential must have a negative serum pregnancy test result within 42 days prior to initiation of study drug.
- Patients with Type 1 diabetes
- Uncontrolled T2DM defined as hemoglobin A_{1c} ($HbA_{1c} \geqslant 9.5\%$) at screening

  Patients with $HbA_{1c} \geq 9.5\%$ may be rescreened.
- Uncontrolled hypertension (systolic ≥ 150 mmHg or diastolic blood pressure ≥ 90 mmHg) at screening or Day 1

  If the initial blood pressure, from the mean of triplicate measurements, is elevated as per the criteria above, the patient may be referred for treatment or adjustment of blood pressure medication by the investigator, and the measurement may be repeated on a different day during the screening period or prior to dosing, in order to determine eligibility.
- Current treatment with obeticholic acid or high-dose vitamin E (≥ 800 IU/day), unless on stable dose of vitamin E ≥ 800 IU/day for at least 6 months prior to screening liver sample collection (archival or fresh) and 6 months prior to randomization
- [redacted]
- Current treatment or treatment that started after the screening liver sample collection (archival or fresh) with thiazolidinediones
- Treatment with metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, insulin, or sodium-glucose transport protein 2 inhibitors unless given at a stable dose (regimen or sliding scale for insulin) for at least 3 months prior to randomization

  For patients with qualifying archival liver biopsy, treatment must be stable from the time of the biopsy to randomization or 3 months prior to randomization, whichever is longer
- Treatment with glucagon-like peptide-1 receptor agonists unless given at a stable dose for at least 3 months prior to randomization

  For patients with qualifying archival liver biopsy, treatment must be stable from the time of biopsy to randomization or 6 months prior to randomization, whichever is longer.
- Treatment with drugs historically associated with NAFLD (e.g., amiodarone, methotrexate, tetracyclines, $sodium\ valproate$ and valproic acid) for more than 2 weeks within the year prior to randomization
- History of Cushing's disease (including pituitary Cushing's disease), diabetes insipidus or other condition causing polyuria and/or polydipsia
- History of adrenal insufficiency or actively taking any form of systemic glucocorticoid at screening
- History of autoimmune endocrinopathy or polyglandular disorder
- History of primary gonadal failure
- History of growth hormone deficiency or acromegaly

- History of Addison's disease
- History of hyper- or hypoparathyroidism
- [redacted]
- Current treatment for [redacted] hypothyroidism [redacted]
- History of liver transplantation
- Confirmed cirrhosis on screening liver sample collection
- Platelet count below 150,000/mm^3
- Evidence of functional hepatic impairment as defined by the presence of any of the following abnormalities:
  - Serum albumin $<$3.5 grams/deciliter (g/dL)
  - International Normalized Ratio (INR) $\geq$1.3 (unless on anticoagulants)
- History of esophageal varices, ascites or hepatic encephalopathy
- *History of any liver disease other than NASH (such as alcoholic liver disease and cirrhosis), except for resolved, self-limited illnesses such as hepatitis A or E, and previous Hepatitis C that meets the Hepatitis C criteria in the next bullet*
- Evidence of other forms of chronic liver disease at screening such as the following:
  - Hepatitis B virus (HBV): patients with active HBV infection (chronic or acute; defined as having positive hepatitis B surface antigen [HBsAg] test at screening)

    Patients with past HBV infection or resolved HBV infection (defined as the as defined by presence of hepatitis B core antibody [HBcAb]; and absence of HBsAg) are eligible if confirmed with negative HBV DNA performed at screening.
  - Positive hepatitis C virus (HCV) antibody test, unless the patient has undetectable HCV RNA levels for $>$6 months and a negative HCV RNA test at screening
  - Evidence of ongoing autoimmune liver disease as defined by compatible liver histology or recent serological markers
  - Known primary biliary cholangitis
  - Primary sclerosing cholangitis
  - *Evidence of or previously diagnosed* Wilson's disease as defined by ceruloplasmin below the limits of normal and compatible liver histology
  - Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level less than normal)
  - History of hemochromatosis or iron overload as defined by the presence of 3+ or 4+ stainable iron on screening liver sample collection (archival or fresh)
  - Drug-induced liver disease as defined on the basis of typical exposure and history
  - Known bile duct obstruction
  - Active history of any other type of liver disease (e.g., liver cancer) other than NASH
- Estimated glomerular filtration rate (eGFR) $<$60 mL/min/1.73m^2
- History of biliary diversion
- Liver enzymes (ALT, AST) levels $>5\times$ upper limit of normal (ULN) at screening. In addition to the two baseline measurements, levels may be repeated once more at the discretion of the investigator during the screening period, and the average of the three readings will be used.

  - Alkaline phosphatase > 2 × ULN at screening. Levels may be repeated once at the discretion of the investigator during the screening period, and the lower of the two readings may be used.
  - Total bilirubin > ULN at screening. Patients with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN; and the subject has normal transaminases, alkaline phosphatase, hemoglobin and reticulocyte count.
- History of eating disorders *within 2 years prior to randomization*
- [redacted]
- Weight gain > 10% or loss > 5% within 3 months prior to randomization
  - For patients with qualifying archival liver biopsies, stable (within 5%) body weight will be required from the time of the biopsy to randomization or 3 months prior to randomization, whichever is longer
- History of procedures for weight loss (e.g., lap band (unless the lap band or balloon was removed and the weight is stable for at least 3 months prior to screening) or gastric bypass)
- Planned medical procedure or surgery during the study *that in* the *investigator's opinion would interfere with participant safety, achieving the study objectives or compliance with the protocol*
- Patients with osteoporosis (T-score of -2.5 or lower)
- History of fracture, bone surgery (e.g., hardware placement, joint replacement, bone grafting, or amputation), or clinically significant bone trauma within 8 weeks of screening
- Vitamin D deficiency (25-hydroxy vitamin D level <20 ng/mL) unless high-dose vitamin D (e.g., 50,000 IU weekly × 6 weeks) is initiated prior to randomization, and vitamin D Institute of Medicine 2011 recommendations (800–2000 IU/day) are followed throughout the study.
- History of osteomalacia
- History of Paget's disease of bone
- History of any other bone diseases which affect bone metabolism (e.g., osteopetrosis, osteogenesis imperfecta)
- Received bone active treatment with the following guidelines:
  - Oral bisphosphonate use > 3 months cumulatively in the past 2 years, OR
  - > 1 month in the past year, OR
  - Any use during the 3-month period prior to *randomization*
- Administration of intravenous bisphosphonate, fluoride, or strontium within the last 5 years *prior to* randomization
- Parathyroid hormone (PTH) or PTH derivatives (e.g., teriparatide, abaloparatide) within the last year *prior to* randomization
- Current or history of treatment with denosumab
- Administration of any of the following treatment within 3 months *prior to randomization*:
  - Any selective estrogen receptor modulator (SERM) (e.g., tamoxifen, raloxifene, and toremifene)
  - Tibolone
  - Anabolic steroids or testosterone
  - Systemic hormone replacement therapy
  - Calcitonin
  - Active Vitamin D analogs (e.g., calcitriol, tacalcitol, paricalcitol, doxercalciferol)

  - Other bone active drugs including anti-convulsants (e.g., phenytoin, carbamazepine, valproate, primidone, and phenobarbital) (except benzodiazepines) and heparin
  - Systemic glucocorticoids, chronic systemic ketoconazole, androgens, adrenocorticotropic hormone (ACTH), cinacalcet, aluminum, lithium, protease inhibitors, gonadotropin-releasing hormone agonists
  - Calcineurin inhibitors
- Treatment with investigational therapy within 30 days or within 5 half-lives of the investigational product, whichever is longer, prior to *randomization*
- Treatment with any biological therapy within 90 days or within 5 half-lives of the biological product, whichever is longer, prior to *randomization*
- Treatment with live, attenuated vaccine within 14 days prior to initiation of study treatment, or anticipation of need of such a vaccine during study treatment or within 6 weeks after the final dose of BFKB8488A, unless specifically reviewed and approved by the investigator
- Illicit drug or marijuana use that would interfere with the conduct of the study in the investigator's judgment; the Medical Monitor should be consulted prior to enrollment for all positive drug screen tests
- Current or history (for a period of more than 3 consecutive months within 1 year prior to screening) of significant alcohol consumption, as defined by either of the following, whichever is the lower amount indicated:
  - Local guidelines (e.g., 2015–2020 Dietary Guidelines for Americans, 8th Edition), or
  - AASLD Diagnosis and Management of NAFLD Practice Guidance (Chalasani et al. 2018), defined as $>$21 standard drinks per week in men and $>$14 standard drinks per week in women, on average
- Current use of more than one pack of cigarettes a day or equivalent nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions
- HIV infection as defined by presence of HIV antibody
- Poor peripheral venous access that precludes acquisition of adequate samples
- *Serious infections* requiring oral or IV antibiotics within 28 days prior to *randomization*
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Blood transfusion within 8 weeks prior to *randomization*
- Donation or loss of blood (excluding the volume of blood that will be drawn during screening procedures) as follows: 50–499 mL of blood within 30 days or $>$499 mL of blood within 56 days prior to study drug administration
- Significant cardiac disease as determined by the investigator, including but not limited to coronary heart disease that is symptomatic or with ongoing ischemia demonstrated by diagnostic testing or having had an event within the past 1 years, unstable angina, congestive heart failure, known arrhythmias of ventricular etiology, unexplained syncope or seizures related to arrhythmia, ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block
- QT interval corrected using Fridericia's formula (QTcF) $>$450 ms in male patients and $>$470 ms in female patients demonstrated by at least two ECGs $>$30 minutes apart

- Baseline PHQ-9 score that is confirmed with a repeat test separated by at least 2 weeks meeting the following criteria:
  - At or above 15 (moderately severe depression), or
  - At or above 10 (moderate depression) and a score of 2 or 3 for the question "Thoughts that you would be better off dead, or thoughts of hurting yourself in some way?"

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (i.e., MRI-PDFF or biopsy) or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 6 weeks after the last patient completes the 52-week treatment period.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 30 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

BFKB8488A will be given at dose levels 50 mg, 75 mg, 100 mg, and [redacted] by subcutaneous injection every 2 weeks for 52 weeks.

Comparator

Placebo will be given by subcutaneous injection every 2 weeks for 52 weeks.

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of BFKB8488A compared with placebo on the basis of the proportion of patients with resolution of NASH and no worsening of fibrosis. The primary and secondary efficacy analyses will be based on a modified intent-to-treat (mITT) approach. All patients who received at least one dose of study drug will be included in the mITT population, with patients grouped according to the treatment assigned at randomization. Analyses will be based on the final biopsy at Week 52 or MRI-PDFF measured over the course of the study.

The final analysis of data from the study will be performed when all patients have either: (i) completed the Week 52 visit and associated liver biopsy or (ii) withdrawn from the study prior to Week 52. The data analysis plan (DAP) will be specified prior to unblinding.

Determination of Sample Size

[redacted] will be enrolled in *two cohorts: 180 patients* in *the fixed dose cohort and* [redacted]. In the four *fixed dose* arms patients are randomized in 1:3:3:2 ratio among 3 *active drug* arms and a placebo *arm*, with approximately 20 patients in the 50 mg BFKB8488A Q2W arm, approximately 60 patients in both the 75 mg BFKB8488A Q2W and 100 mg BFKB8488A Q2W arm and approximately 40 in the placebo arm. [redacted]. There is ≥90% power to detect a 30% increase in resolution of NASH, assuming a 15% placebo rate, a type I error rate of 0.05, a two sided test of proportions and 10% lost to follow-up comparing any single arm, with the exception of the 50-mg arm, to the pooled placebo arms. The 50-mg arm, under the same assumptions and a sample size of 20, will have 76% power. *The fixed dose cohort alone, under the same assumptions, has a power of 87% comparing the 75-mg arm or 100-mg arm to the placebo arm and a power of 66% for the 50-mg arm.*

Interim Analyses

A single planned interim analysis will be conducted when at least [redacted] of the patients in the fixed dose arms have completed the Week 16 MRI-PDFF. The interim analysis results will be reviewed. A DAP will be drafted prior to the interim, including the variables that will be assessed by treatment arm as well as a list of individuals who will be unblinded including the IMC.

The Sponsor may choose to conduct interim efficacy analyses of select endpoints. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be reviewed by an IMC. Details of the interim will be pre-specified in the DAP prior to review by the IMC.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
A1AT	Alpha-1-antitrypsin
AASLD	American Association for the Study of Liver Disease
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
BLM	baseline measurement
C-SSRS	Columbia-Suicide Severity Rating Scale
CAP	controlled attenuation parameter
CRF	Case Report Form
CRN	Clinical Research Network
CRO	contract research organization
DAP	data analysis plan
DXA	dual-energy X-ray absorptiometry
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
Fab	fragment antigen binding
Fc	fragment crystallizable
FDA	Food and Drug Administration
FFA	free fatty acid
FGFR1	fibroblast growth factor receptor 1c
GI	gastrointestinal
HbA_{1c}	hemoglobin A_{1c}
HBsAg	hepatitis B surface antigen
HBcAb	total hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HPA	hypothalamic- pituitary- adrenal
ICH	International Council for Harmonisation
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IRF	independent review facility
IxRS	interactive voice or web-based response system

Abbreviation	Definition
KLB	Klotho β
mg/dL	milligrams/deciliter
mITT	modified intent-to-treat
MRI-PDFF	magnetic resonance imaging-derived proton density fat fraction
NAFLD	non-alcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	non-alcoholic steatohepatitis
NGS	next-generation sequencing
PD	pharmacodynamic
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic
PRO	patient-reported outcome
PTH	parathyroid hormone
Q2W	every 2 weeks
Q4W	every 4 weeks
QTcF	QT interval corrected through use of Fridericia's formula
QW	weekly
RBR	Research Biosample Repository
SERM	selective estrogen receptor modulator
SIB	suicidal ideation and behavior
T2DM	type 2 diabetes mellitus
TSH	thyroid–stimulating hormone
UFC	urinary free cortisol
ULN	upper limit of normal
VAS	Visual Analogue Scale
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON NON-ALCOHOLIC STEATOHEPATITIS

Non-alcoholic steatohepatitis (NASH) is a condition stemming from excess liver fat in combination with hepatic inflammation and cell damage. Despite limited epidemiological data, the estimated prevalence of NASH in the general population ranges between 1.5% and 6.45% (Younossi et al. 2016).

NASH poses a significant burden to both the patient and the healthcare system. Patients with NASH typically present with comorbid metabolic syndrome. Associated conditions that are considered risk factors for NASH include obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia. Considering the current obesity epidemic in the United States, NASH incidence is expected to increase over time.

Furthermore, NASH can progress to fibrosis, and eventually cirrhosis and hepatocellular carcinoma. The degree of fibrosis determines NASH stage, and time to progression is typically 7 years per fibrosis stage (Singh et al. 2015). Patients in the earlier fibrosis stages may be treated by their primary care provider or endocrinologist, but those who progress to the higher stages may require more specialized care from a hepatologist. NASH-related cirrhosis is currently the second leading indication for liver transplants in the United States (Wong et al. 2015).

The American Association for the Study of Liver Disease (AASLD) recommends managing NASH by treating liver disease as well as the associated metabolic comorbidities mentioned above (Chalasani et al. 2018). Available treatment modalities include lifestyle interventions and bariatric surgery (in eligible obese individuals), but none of the current non-pharmacologic options have demonstrated efficacy in NASH. Pharmacologic treatments such as thiazolidinediones, vitamin E, metformin, bile acid sequestrants, and omega-3 fatty acids have been either ineffective in the treatment of NASH or undesirable due to their side effect profiles (Patel et al. 2015; Singh et al. 2017). At present, no pharmacologic agents are approved by regulatory agencies for the treatment of NASH.

1.2 BACKGROUND ON BFKB8488A

BFKB8488A is a full-length, Chinese hamster ovary cell-derived, humanized agonistic bispecific antibody targeting cells expressing both fibroblast growth factor receptor 1c (FGFR1) and Klotho β (KLB), most significantly adipocytes. One fragment antigen-binding (Fab) region of the antibody is directed against the extracellular domain of KLB. The other Fab is directed against the extracellular domain of FGFR1. Heterodimerization of the two half-antibodies is driven by "knob" and "hole" modifications of the CH3 domain of the Fc region (Atwell et al. 1997; Spiess et al. 2013). BFKB8488A contains the N296G and N300G amino acid substitutions in the fragment crystallizable (Fc) regions for the "knob" and "hole," respectively, which results in non-glycosylated

heavy chains that have minimal binding to Fcγ receptors and, consequently, prevents Fc-effector function.

To avoid non-selective activation of FGFR1 and its potentially adverse consequences (Wu et al. 2013), this bispecific antibody was designed to specifically activate only the FGFR1/KLB complex. Activation of the FGFR1/KLB complex in adipose tissues by FGF21 analogs or by agonistic antibodies has been proposed as a therapeutic strategy for treatment of obesity-associated metabolic derangements including hepatosteatosis, dyslipidemia, T2DM, insulin resistance, and hyperglycemia (Foltz et al. 2012; Kolumam et al. 2015). Anticipated beneficial effects include insulin sensitization, increased energy expenditure, and reduction of ectopic fat deposits. Based on this, BFKB8488A is being developed as a therapy for NASH.

Results from Study GC29819, a Phase Ia, placebo-controlled, single-dose study in otherwise healthy overweight and obese volunteers with likely insulin resistance showed that BFKB8488A had acceptable tolerability at single SC doses of up to 342 mg. At the highest SC dose (681 mg), 6 out of 8 subjects reported adverse events of mild to moderate nausea. Based on these gastrointestinal adverse events, a single dose of 681-mg dose is considered non-tolerated, and a single dose of 342 mg was considered to be the maximum tolerated dose in the study. There were no serious adverse events, dose-limiting adverse events, or discontinuations due to adverse events.

In the ongoing Phase Ib Study GC39547 (a randomized, blinded, placebo-controlled, multiple ascending dose study in patients with T2DM and patients with non-alcoholic fatty liver disease [NAFLD]), an acceptable safety and tolerability profile for BFKB8488A has been observed in patients treated with BFKB8488A doses up to 50 mg SC weekly (QW), [redacted] SC every 2 weeks (Q2W), and 100 mg SC every 4 weeks (Q4W).

Refer to the BKFB8488A Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The available nonclinical data for BFKB8488A are consistent with the expected pharmacologic activity of BFKB8488A to mimic certain metabolic activities of recombinant FGF21 via selective activation of FGFR1/KLB but not FGFR2/KLB or FGFR3/KLB complexes. The therapeutic strategy of BFKB8488A thus involves selective activation of the FGFR1/KLB complex while minimizing the interference of endogenous FGF signaling. Previously reported clinical activity of FGF21 analogs in overweight individuals with T2DM suggested weight loss, glucose and insulin lowering, and other metabolic benefits as well as side effects (Gaich et al. 2013; Calle et al. 2014; Talukdar et al. 2016).

In the preliminary data from a Phase II study in patients with NASH, BMS-986036 (pegylated FGF21) significantly decreased hepatic fat fraction (Sanyal et al. 2017). The pegylated analog of FGF21 also improved biomarkers of fibrosis (magnetic resonance elastography [MRE] and pro-C3), adiponectin, and markers of hepatic injury (ALT and AST). These results, presented at the European Association for the Study of the Liver (EASL) 2017, suggest that a molecule that mimics FGF21 activity would potentially improve steatosis, liver injury, and fibrosis in NASH.

BFKB8488A is hypothesized to directly and indirectly improve NASH via multiple mechanisms. BFKB8488A can potentially reduce hepatic fat by suppressing de novo lipogenesis and gluconeogenesis in the liver and reduce hepatic free fatty acid (FFA) uptake through suppressing adipose tissue lipolysis. In turn, removal of liver fat may improve NAFLD activity score (NAS) and fibrosis in patients with NASH.

The molecule may work on various target organs that indirectly affect hepatic steatosis. BFKB8488A may work on the nervous system to increase energy expenditure, decrease hunger, and decrease sweets and alcohol preference. By reducing food and sugar intake, the molecule may increase FFA oxidation. In genetic loss-of-function studies in the mouse model, KLB in neurons was essential for FGF21 to cause weight loss and lower glucose and insulin levels (Lan et al. 2017). In the same studies, the FGF21 mimetic antibody that activates FGFR1/KLB also required neuronal KLB for its metabolic effects.

In the Phase Ia study (GC29819) in overweight or obese, otherwise healthy subjects, BFKB8488A increased plasma adiponectin, lowered fasting plasma insulin, and decreased serum triglycerides following single doses of BFKB8488A over a range of doses (Arora et al. 2017a; Arora et al. 2017b). These observed effects of BFKB8488A might be mediated by an improvement in adipose tissue function. Improving adipose tissue function and preventing overnutrition may restore metabolic homeostasis and prevent/reverse the fibrotic liver damage caused by ectopic fat deposition. BFKB8488A may also alter pancreatic enzyme secretion in the pancreas, and consequently reduce nutrient absorption in the gut. By the aforementioned mechanisms, the drug may reduce body weight and prevent weight gain, increase metabolic rate, and improve insulin sensitivity and lipid profile, with a safety profile potentially equivalent or superior to glucagon-like peptide-1 receptor agonists. As an agent that has the potential to treat fatty liver changes as well as metabolic comorbidities, BFKB8488A may become a therapeutic option for the treatment of NASH.

Clinical experience with BFKB8488A to date has not generated safety concerns that would preclude further evaluation in patients. In Study GC29819, there were no deaths, serious adverse events, hypersensitivity reactions, or withdrawals due to adverse events and no dose-limiting adverse events as defined in the protocol. One adverse event of special interest of weight decrease was reported in a subject who received BFKB8488A at the highest dose (681 mg SC). Moderate gastrointestinal (GI) symptoms (nausea,

vomiting, diarrhea and abdominal distension) seen at the highest dose (681 mg SC) determined tolerability, making 342 mg the maximum tolerated dose (MTD) currently tested. All GI manifestations were manageable and reversible. In the ongoing Phase Ib Study GC39547, based on preliminary data, there have been no deaths related to the study drug. One serious adverse event of Grade 3 gastritis, suspected to be related to the study drug by the Investigator, was reported in a single patient and has resolved.

Study GC41033 includes patients with NASH, many of whom may also have concomitant type 2 diabetes, obesity, and hypertension. In the setting of the COVID-19 pandemic, patients with metabolic diseases, such as obesity (Hendren et al. 2020); Type 2 diabetes (Williamson et al. 2020); and chronic liver diseases, such as NASH and cirrhosis (Ji et al. 2020; Wang et al. 2020; Zheng et al. 2020) are considered vulnerable populations, due to a higher potential for progression to severe COVID-19, serious complications, and longer viral shedding time. As BFKB8488A is in early clinical development, it is not known whether or how BFKB8488A treatment impacts the incidence or severity of COVID-19. Based on the mechanism of action of BFKB8488A, it is not anticipated that it will increase the risk or the severity of infection with SARS-CoV-2. Clinical trials with BFKB8488A have been ongoing during this pandemic and, although the study numbers are small, no patients receiving BFKB8488A have developed COVID-19. Some of the symptoms associated with COVID-19 (e.g., nausea, vomiting, and diarrhea) are also adverse events that have been reported with BFKB8488A at frequencies higher than 10%. In the event of potential overlapping toxicity for these events, the current protocol management guidelines clearly lay out criteria for drug interruption and discontinuation. Additionally, the protocol recommends interruption for study drug in instances of any National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 adverse events and discontinuation if they do not resolve to Grade 1 with symptomatic treatment or standard of care. The protocol also mandates study drug discontinuation for all CTCAE Grade 4 events, regardless of attribution. The sites will be instructed to follow local guidelines and standard of care for preventing and managing COVID-19 infection. [redacted]

In summary, the aim of this study is to determine if BFKB8488A can effectively treat patients with NASH. Several measures will be taken to ensure the safety of patients participating in this study based on the potential risks for BFKB8488A based on nonclinical and clinical studies and published literature (see Section 5.1.1). Eligibility criteria have been designed to exclude patients at higher risk for potential toxicities (see Section 4.1). In addition, safety objectives have been established to monitor for potential toxicities.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of BFKB8488A compared with placebo in patients with NASH. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of BFKB8488A compared with placebo on the basis of the following endpoint:

- Proportion of patients with resolution of NASH on overall histopathological reading, without worsening of fibrosis at Week 52. Resolution of NASH is defined as a NAS of 0–1 for inflammation, 0 for ballooning, and any value for steatosis as determined by a central reader. Worsening of fibrosis is defined as any increase in NASH Clinical Research Network (CRN) fibrosis stage as determined by a central reader.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of BFKB8488A compared with placebo on the basis of the following endpoints:

- Change from baseline in hepatic fat fraction as assessed by magnetic resonance imaging–derived proton density fat fraction (MRI-PDFF) at Week 52
- Proportion of patients with improvement in liver histology from baseline, defined as $\geq$ 2 points reduction in NAS with at least a 1-point reduction in either lobular inflammation or hepatocellular ballooning AND no worsening of fibrosis stage as determined by a central reader at Week 52
- Proportion of patients with improvement in liver fibrosis greater than or equal to one stage (as defined by the NASH CRN fibrosis stage) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis), determined by a central reader at Week 52

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of BFKB8488A compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grading scale
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to evaluate the BFKB8488A PK profile on the basis of the following endpoint:

- Serum concentration of BFKB8488A at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to BFKB8488A on the basis of the following endpoint:

- Incidence of anti-drug antibodies (ADAs) during the study relative to the prevalence of ADAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, exploratory biomarker, or PK endpoints

2.5 BIOMARKER OBJECTIVES

The exploratory biomarker objectives for this study are the following:

- To identify biomarkers that are predictive of response to BFKB8488A (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of BFKB8488A activity (i.e., pharmacodynamic [PD] biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoint:
  - Relationship between MRI-derived biomarkers, adipokines, triglycerides, lipids, liver enzymes, pro-C3, and other biomarkers in blood and tissue samples and efficacy, safety, and PK
- To predict or evaluate histologic changes in response to BFKB8488A on the basis of the following endpoint:
  - Automated image analysis of H&E and trichrome-stained liver biopsies

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to assess the patient perspective on response to BFKB8488A on the basis of the following endpoint:

- Change from baseline in Appetite Sensations Visual Analogue Scale (VAS) scores at specified timepoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase II, randomized, parallel-group, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, and pharmacokinetics of BFKB8488A compared with placebo in patients with NASH. [redacted] as determined by the Sponsor's Internal Monitoring Committee [IMC]; see Section 3.1.2 for additional details) will be enrolled at multiple investigational sites across the globe. Patients will be randomly assigned to receive either BFKB8488A or placebo *in the* fixed *dosing cohort* [redacted] In the fixed dose arms, patients will be randomly assigned to receive BFKB8488A 50 mg, BFKB8488A 75 mg, BFKB8488A 100 mg, or placebo. [redacted] Randomized patients will be stratified by diabetes status and fibrosis stage (F1 vs. F2/F3). A maximum of up to approximately 20% of patients with F1 will be enrolled in this study.

The study will consist of a screening period (up to 8 weeks; including an initial screening and a main screening), a subsequent 52-week treatment period, and a 6-week safety follow-up period. The total duration of the study for each patient will be approximately 66 weeks.

During screening (up to 8 weeks), eligibility screening assessments should be completed as early as possible. All eligibility assessments must be completed within the 8-week screening period with the exception of delays in laboratory (including biopsy) and MRI reporting or due to unforeseen scheduling issues. All eligibility assessments should be completed prior to randomization.

Patients will be required to undergo a liver biopsy prior to randomization in order to confirm diagnosis of NASH. An archival liver sample collected within 6 months prior to randomization may be used provided it meets eligibility requirements (see Section 4.1); otherwise, a fresh biopsy will be taken during the screening period.

To ensure an accurate baseline, two measurements will be taken for AST and ALT for all patients, first during the initial screening and then during the main screening approximately 4 weeks later (at least 2 weeks apart). A Fibroscan® assessment will also be performed during the initial screening to establish a baseline for all patients*; a*

[redacted] The initial screening and the main screening may overlap; assessments for the initial screening and main screening may be done at the same time.

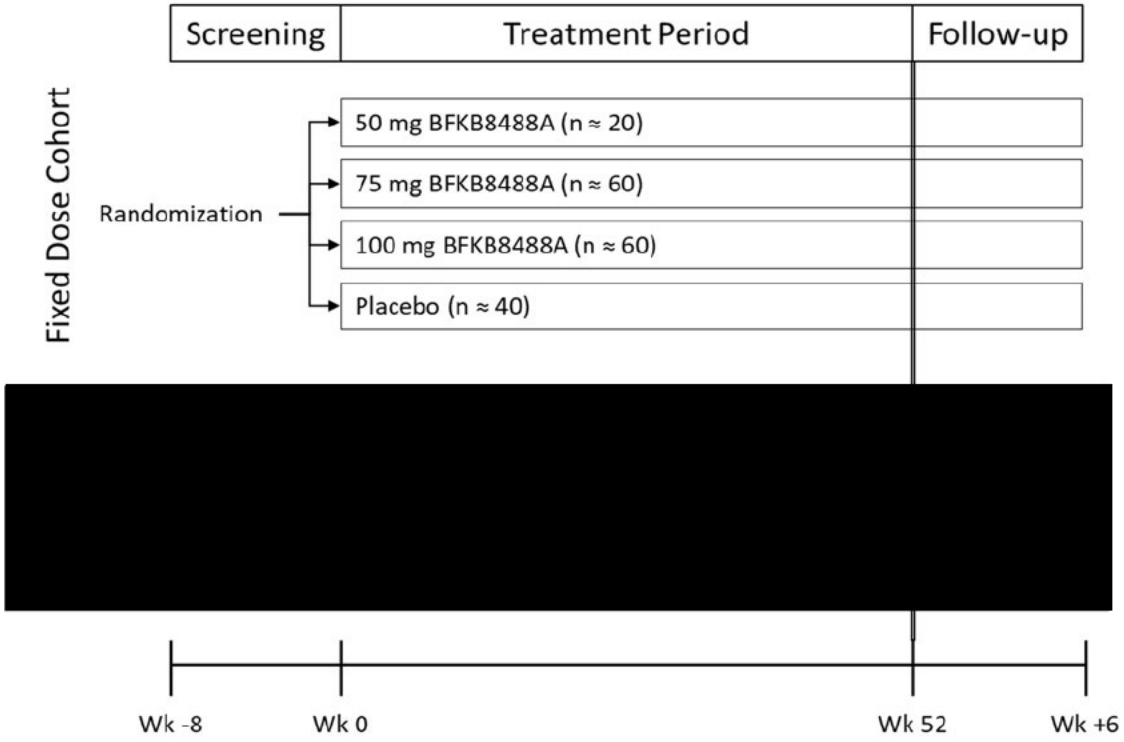
If a patient does not meet all eligibility criteria within the screening period *(with up to 2 week allowance for delays in laboratory (including biopsy) and MRI reporting or unforeseen scheduling issues*), re-screening is permitted once, at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 8 weeks after previously signing the consent form. The investigator will record reasons for screen failure in the screening log (see Section 4.5.1 and Section 8.1). Re-screening patients must meet all eligibility criteria. Labs and tests performed within the last 8 weeks prior to re-screening do not need to be repeated (except pregnancy tests, insulin, lipids, AST/ALT, and HbA_{1c}, unless approved by the Medical Monitor). [redacted] The biopsy will not need to be repeated if an archival sample is available from a biopsy performed no more than 6 months before randomization. [redacted]

In order to establish a stable baseline for the study, all patients must be compliant with current medication and avoid any atypical physical activity for the week immediately prior to randomization. In addition, patients will be instructed to adhere to a diet consistent with guidelines for weight maintenance and a healthy lifestyle. These instructions should be given to the patients as early as possible during the screening period.

During the treatment period, patients will receive Q2W SC injections of BFKB8488A or placebo. Patients will receive a total of 26 (Q2W) doses.

Patients who complete the treatment period or discontinue treatment early will enter a follow-up period for a total of 6 weeks. Patients will be asked to come in for follow-up and evaluation as described in the schedule of activities.

Figure 1 Study Schema



Wk=Week

[redacted]

[redacted]

3.1.2 Internal Monitoring Committee

The incidence and nature of any adverse events, serious adverse events, and laboratory abnormalities will be assessed on an ongoing basis by the Sponsor's IMC. This committee will not be blinded to treatment assignments, and will include a medical monitor, drug safety scientist, and biostatistician from the Sponsor. The PI, site investigators, and site personnel will remain blinded until the completion of the study, except in circumstances where unblinding is determined by the investigator or by the IMC to be important for the safety of a patient. The IMC may request that additional Sponsor scientists (e.g., PK or clinical scientists) participate in data analysis either blinded or unblinded. Members of the IMC will be independent of the operational team responsible for executing the study.

The IMC will review cumulative unblinded safety data at regular intervals during the study. In addition, the IMC will conduct the interim analysis of the efficacy data as needed. Ad hoc meetings may be called in addition to scheduled meetings to help evaluate, and provide recommendations for management of, any emerging potential safety signals. During periodic blinded safety analyses, events that would trigger an ad hoc IMC meeting and review of unblinded data to decide the safety of continuing the study include, but are not limited to, the following:

- Three patients develop the same Grade 3 CTCAE attributed to study drug OR
- Two patients develop any Grade 4 CTCAE attributed to study drug OR
- One patient develops a Grade 5 CTCAE

After reviewing the data, the IMC may make recommendations such as the following:

- The study will continue as planned
- The study will continue with a change in dose level [redacted] or frequency within a treatment arm

  In cases where a dose level or frequency is changed during the study, the IMC may recommend that the study team consider adding up to 30 additional patients to the study, in order to ensure that an adequate number of patients receive the changed dose for an adequate duration.

[redacted]

- The study will continue with discontinuation of enrollment in a treatment arm
- The study will stop for unfavorable benefit-risk
- Additional analyses will need to be performed
- Enrollment will be held pending further safety evaluation

Specific operational details such as committee composition, frequency and timing of meeting, and member roles and responsibility of the IMC will be detailed in a separate IMC charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (i.e., MRI-PDFF or biopsy) or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 6 weeks after the last patient completes the 52-week treatment period.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 30 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for BFKB8488A Dose and Schedule

In the proposed Phase II study in patients with NASH, [redacted] dosing paradigms will be evaluated: fixed dosing [redacted]. These dosing paradigms will be explored in light of the considerable variability observed in patient PK, PD, and tolerability in the Phase I studies in order to determine how to best optimize the benefit-risk of BFKB8488A treatment on both the patient and population levels.

The fixed dose regimens of 50 mg Q2W, 75 mg Q2W, and 100 mg Q2W were selected on the basis of the Phase I PK, PD, and safety and tolerability results. In preliminary results from the Phase Ib (GC39547) study, mean relative decreases in liver fat from baseline (as measured by MRI-PDFF) of 6.2%, 23%, and 41% were observed in patients with NAFLD who were treated with 50, 75, and 100 mg BFKB8488A Q2W, respectively, for 12 weeks compared with a decrease of 2.2% in patients treated with placebo. A decrease in liver fat after 12 weeks of treatment is expected to be associated with improvement in NASH-related endpoints after 52 weeks of treatment; hence, these dosing regimens are expected to be efficacious in some proportion of patients with NASH in the Phase II study. Doses of 50, 75, and 100 mg BFKB8488A Q2W were tolerated in the Phase Ib study and are expected to be tolerated in the proposed Phase II study as well.

[redacted]

[redacted]

The evaluation of [redacted] different dosing paradigms (fixed and [redacted]) across the range of doses proposed (50 mg Q2W, 75 mg Q2W, 100 mg Q2W, [redacted]) is expected to provide valuable information as to how best to administer BFKB8488A to maximize the benefit-risk ratio [redacted] NASH patient population as a whole.

3.3.2 Rationale for Patient Population

Patients with biopsy-confirmed NASH, with a NAS $\geq$ 4 and Fibrosis Stage 1, 2, or 3, have been chosen for this study in order to assess the effects of BFKB8488A. These patients have significant disease but the damage may still be reversible as they have not yet progressed to cirrhosis. These patients are expected to be representative of the population which would derive the greatest benefit from a NASH treatment should one be approved.

3.3.3 Rationale for Control Group

Overall, patients enrolled in this study will be randomly assigned in a 10:3 ratio to receive BFKB8488A or matching placebo. Patients in the fixed dose arms will be randomly assigned in a 1:3:3:2 ratio to receive either fixed doses of BFKB8488A 50 mg, BFKB8488A 75 mg, BFKB8488A 100 mg, or matching placebo. [redacted] Placebo-treated control groups will be used in this study to assess differences in histological endpoints defining NASH and fibrosis, liver fat as assessed by MRI-PDFF, and safety in patients who receive BFKB8488A compared with patients who receive placebo. The two placebo arms are separated to preserve blinding in the variable dosing arm, and, other than adjustment of placebo administered, are identical and can be pooled for analysis. The use of a control group is necessary given the inherent variability in response due to lifestyle changes, sustained weight loss, and other factors that may contribute to a placebo response.

All patients enrolled in the study, including those randomly assigned to receive placebo, will be provided with adequate counseling regarding patient lifestyle changes around diet and activity as described in Section 4.4.3. Therefore, patients assigned to placebo may benefit from participation in the study.

3.3.4 Rationale for PK Sampling Schedule

The sampling schedule specified in the protocol is designed to capture data to enable characterization of the pharmacokinetic profile of BFKB8488A, including the potential impact of ADA on pharmacokinetics, and consists of pre-dose serum collections after initial doses and at steady-state, and a post-dose serum collection at steady-state.

3.3.5 Rationale for Biomarker Assessments

Clinical toxicity may not be a reliable surrogate of target modulation by BFKB8488A. Therefore, PD biomarkers will be measured in plasma, serum and other samples to determine whether clinically achievable exposures are sufficient for producing the desired effect on the intended molecular target.

NASH is a heterogeneous disease, and the expression of both the endogenous ligand for FGFR1-KLB as well as KLB receptor expression on target tissues has been shown to vary among patients with metabolic dysfunction (Roesch et al. 2015). Therefore, all patients may not be equally likely to benefit from treatment with BFKB8488A. Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients with defects in endogenous FGF21 pathways that may be more likely to respond to BFKB8488A. PD biomarkers will be assessed to demonstrate evidence of biologic activity of BFKB8488A in patients, to support selection of a recommended dose and dosing regimen, and to inform potential revisions to the PK sample collection schedule.

Tissue samples will be collected for DNA extraction to enable whole genome sequencing (WGS) or whole exome sequencing (WES) to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

4. MATERIALS AND METHODS

4.1 PATIENTS

[redacted] as determined by the IMC, see Section 3.1.2 for additional details).

4.1.1 Inclusion Criteria

- Signed Informed Consent Form

[redacted]

- AST ≥ 20
- FibroScan® fibrosis result ≥ 7.0 kilopascals (kPa)
- FibroScan® controlled attenuation parameter (CAP) ≥ 285 decibels per meter (dB/m)

Patients must meet the following criteria during the main screening for study entry:

- Age ≥ 18 and ≤ 75 years at time of signing Informed Consent Form
- Ability to comply with the study protocol (including ability to safely obtain a liver biopsy if needed), in the investigator's judgment
- Hepatic steatosis on MRI ($\geq 8\%$ average liver PDFF) prior to randomization
- Confirmed diagnosis of NASH as documented through central testing of a representative liver sample performed no more than 6 months before randomization, with a NAS greater than or equal to 4 with at least 1 point each in inflammation and ballooning along with a NASH CRN fibrosis score between F1 and F3 (a maximum of approximately 20% of patients with F1 will be enrolled). The biopsy must be performed while the patient is not on any treatment prescribed for the purpose of this study or on any investigational therapy for the treatment of NASH.

If an archival liver sample is unavailable or does not meet eligibility criteria, liver tissue must be obtained from a biopsy performed at screening.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use a contraceptive method with a failure rate of $<1\%$ per year during the treatment period and for at least 42 days after the final dose of study drug. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for at least 132 days after the final dose of study drug. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for the duration of the pregnancy to avoid exposing the embryo.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Inability to undergo an MRI for any reason (such as metal implants or devices, claustrophobia, and/or patient size
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 42 days after the final dose of BFKB8488A

  Women of childbearing potential must have a negative serum pregnancy test result within 42 days prior to initiation of study drug.
- Patients with Type 1 diabetes
- Uncontrolled T2DM defined as hemoglobin A_{1c} ($HbA_{1c} \geq 9.5\%$) at screening

  Patients with $HbA_{1c} \geq 9.5\%$ may be rescreened.
- Uncontrolled hypertension (systolic $\geq$ 150 mmHg or diastolic blood pressure $\geq$ 90 mmHg) at screening or Day 1

  If the initial blood pressure, from the mean of triplicate measurements, is elevated as per the criteria above, the patient may be referred for treatment or adjustment of blood pressure medication by the investigator, and the measurement may be repeated on a different day during the screening period or prior to dosing, in order to determine eligibility. *See Section 4.5.4 for guidance on blood pressure measurement.*
- Current treatment with obeticholic acid or high-dose vitamin E ($\geq$800 IU/day), unless on stable dose of vitamin E $\geq$800 IU/day for at least 6 months prior to screening liver sample collection (archival or fresh) and 6 months prior to randomization
- [redacted]
- Current treatment or treatment that started after the screening liver sample collection (archival or fresh) with thiazolidinediones
- Treatment with metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, insulin, or sodium-glucose transport protein 2 inhibitors unless given at a stable dose (regimen or sliding scale for insulin) for at least 3 months prior to randomization

  For patients with qualifying archival liver biopsy, treatment must be stable from the time of the biopsy to randomization or 3 months prior to randomization, whichever is longer.
- Treatment with glucagon-like peptide-1 receptor agonists unless given at a stable dose for at least 3 months prior to randomization

  For patients with qualifying archival liver biopsy, treatment must be stable from the time of biopsy to randomization or 6 months prior to randomization, whichever is longer.

- Treatment with drugs historically associated with NAFLD (e.g., amiodarone, methotrexate, tetracyclines, *sodium valproate* and valproic acid) for more than 2 weeks within the year prior to randomization
- History of Cushing's disease (including pituitary Cushing's disease), diabetes insipidus or other condition causing polyuria and/or polydipsia
- History of adrenal insufficiency or actively taking any form of systemic glucocorticoid at screening
- History of autoimmune endocrinopathy or polyglandular disorder
- History of primary gonadal failure
- History of growth hormone deficiency or acromegaly
- History of Addison's disease
- History of hyper- or hypoparathyroidism
- [redacted]
- [redacted]
- History of liver transplantation
- Confirmed cirrhosis on screening liver sample collection
- Platelet count below 150,000/mm^3
- Evidence of functional hepatic impairment as defined by the presence of any of the following abnormalities:
  - Serum albumin < 3.5 grams/deciliter (g/dL)
  - International Normalized Ratio (INR) ≥ 1.3 (unless on anticoagulants)
- History of esophageal varices, ascites or hepatic encephalopathy
- *History of any liver disease other than NASH (such as alcoholic liver disease and cirrhosis), except for resolved, self-limited illnesses such as hepatitis A or E, and previous Hepatitis C that meets the Hepatitis C criteria in the next bullet*
- Evidence of other forms of chronic liver disease at screening such as the following:
  - Hepatitis B virus (HBV): patients with active HBV infection (chronic or acute; defined as having positive hepatitis B surface antigen [HBsAg] test at screening)

    Patients with past HBV infection or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible if confirmed with negative HBV DNA performed at screening.

  - Positive hepatitis C virus (HCV) antibody test, unless the patient has undetectable HCV RNA levels for >6 months and a negative HCV RNA test at screening
  - Evidence of ongoing autoimmune liver disease as defined by compatible liver histology or recent serological markers
  - Known primary biliary cholangitis
  - Primary sclerosing cholangitis
  - *Evidence of or previously diagnosed* Wilson's disease as defined by ceruloplasmin below the limits of normal and compatible liver histology
  - Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by A1AT level less than normal)
  - History of hemochromatosis or iron overload as defined by the presence of 3+ or 4+ stainable iron on screening liver sample collection (archival or fresh)
  - Drug-induced liver disease as defined on the basis of typical exposure and history
  - Known bile duct obstruction
  - Active history of any other type of liver disease (e.g., liver cancer) other than NASH
- Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2
- History of biliary diversion
- Liver enzymes (ALT, AST) levels $>5\times$ upper limit of normal (ULN) at screening. In addition to the two baseline measurements, levels may be repeated once more at the discretion of the investigator during the screening period, and the average of the three readings will be used.
  - Alkaline phosphatase $>2\times$ ULN at screening. Levels may be repeated once at the discretion of the investigator during the screening period, and the lower of the two readings may be used.
  - Total bilirubin $>$ ULN at screening. Patients with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is $\leq$ ULN; and the subject has normal transaminases, alkaline phosphatase, hemoglobin and reticulocyte count.
- History of eating disorders *within 2 years prior to randomization*

[redacted]

- Weight gain $>10\%$ or loss $>5\%$ within 3 months prior to randomization

  - For patients with qualifying archival liver biopsies, stable (within 5%) body weight will be required from the time of the biopsy to randomization or 3 months prior to randomization, whichever is longer
- History of procedures for weight loss (e.g., lap band (unless the lap band or balloon was removed and the weight is stable for at least 3 months prior to screening) or gastric bypass)
- Planned medical procedure or surgery during the study *that in* the *investigator's opinion would interfere with participant safety, achieving the study objectives or compliance with the protocol*
- Patients with osteoporosis (T-score of -2.5 or lower)
- History of fracture, bone surgery (e.g., hardware placement, joint replacement, bone grafting, or amputation), or clinically significant bone trauma within 8 weeks of screening
- Vitamin D deficiency (25-hydroxy vitamin D level $<$20 ng/mL) unless high-dose vitamin D (e.g., 50,000 IU weekly $\times$ 6 weeks) is initiated prior to randomization, and vitamin D Institute of Medicine 2011 recommendations (800–2000 IU/day) are followed throughout the study.
- History of osteomalacia
- History of Paget's disease of bone
- History of any other bone diseases which affect bone metabolism (e.g., osteopetrosis, osteogenesis imperfecta)
- Received bone active treatment with the following guidelines:
  - Oral bisphosphonate use $>$ 3 months cumulatively in the past 2 years, OR
  - $>$ 1 month in the past year, OR
  - Any use during the 3-month period prior to *randomization*
- Administration of intravenous bisphosphonate, fluoride, or strontium within the last 5 years *prior to* randomization
- Parathyroid hormone (PTH) or PTH derivatives (e.g., teriparatide, abaloparatide) within the last year *prior to* randomization
- Current or history of treatment with denosumab
- Administration of any of the following treatment within 3 months *prior to randomization*:
  - Any selective estrogen receptor modulator (SERM) (e.g., tamoxifen, raloxifene, and toremifene)
  - Tibolone
  - Anabolic steroids or testosterone
  - Systemic hormone replacement therapy
  - Calcitonin

  - Active Vitamin D analogs (e.g., calcitriol, tacalcitol, paricalcitol, doxercalciferol)
  - Other bone active drugs including anti-convulsants (e.g., phenytoin, carbamazepine, valproate, primidone, and phenobarbital) (except benzodiazepines) and heparin
  - Systemic glucocorticoids, chronic systemic ketoconazole, androgens, adrenocorticotropic hormone (ACTH), cinacalcet, aluminum, lithium, protease inhibitors, gonadotropin-releasing hormone agonists
  - Calcineurin inhibitors
- Treatment with investigational therapy within 30 days or within 5 half-lives of the investigational product, whichever is longer, prior to *randomization*
- Treatment with any biological therapy within 90 days or within 5 half-lives of the biological product, whichever is longer, prior to *randomization*
- Treatment with live, attenuated vaccine within 14 days prior to initiation of study treatment, or anticipation of need of such a vaccine during study treatment or within 6 weeks after the final dose of BFKB8488A, unless specifically reviewed and approved by the investigator
- Illicit drug or marijuana use that would interfere with the conduct of the study in the investigator's judgment; the Medical Monitor should be consulted prior to enrollment for all positive drug screen tests
- Current or history (for a period of more than 3 consecutive months within 1 year prior to screening) of significant alcohol consumption, as defined by either of the following, whichever is the lower amount indicated:
  - Local guidelines (e.g., 2015–2020 Dietary Guidelines for Americans, 8th Edition), or
  - AASLD Diagnosis and Management of NAFLD Practice Guidance (Chalasani et al. 2018), defined as $>$21 standard drinks per week in men and $>$14 standard drinks per week in women, on average
- Current use of more than one pack of cigarettes a day or equivalent nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum)
- History of severe allergic, anaphylactic, or other hypersensitivity reactions
- HIV infection as defined by presence of HIV antibody
- Poor peripheral venous access that precludes acquisition of adequate samples
- *Serious infections* requiring oral or IV antibiotics within 28 days prior to *randomization*
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Blood transfusion within 8 weeks prior to *randomization*

- Donation or loss of blood (excluding the volume of blood that will be drawn during screening procedures) as follows: 50–499 mL of blood within 30 days or >499 mL of blood within 56 days prior to study drug administration
- Significant cardiac disease as determined by the investigator, including but not limited to coronary heart disease that is symptomatic or with ongoing ischemia demonstrated by diagnostic testing or having had an event within the past 1 years, unstable angina, congestive heart failure, known arrhythmias of ventricular etiology, unexplained syncope or seizures related to arrhythmia, ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block
- QT interval corrected using Fridericia's formula (QTcF) >450 ms in male patients and >470 ms in female patients demonstrated by at least two ECGs >30 minutes apart
- Baseline PHQ-9 score that is confirmed with a repeat test separated by at least 2 weeks meeting the following criteria:
  - At or above 15 (moderately severe depression), or
  - At or above 10 (moderate depression) and a score of 2 or 3 for the question "Thoughts that you would be better off dead, or thoughts of hurting yourself in some way?"

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

Patients will be randomized to the treatment arms through an interactive voice or web-based response system (IxRS). After written informed consent has been obtained, all patients will receive a screening number, which will be assigned by the IxRS. Following completion of the screening period and after all patient eligibility requirements are confirmed on Day 1, patients will be assigned an identification number (a different number from the screening number) and will be randomized to one of the six study arms (fixed dose arms: 50 mg BFKB8488A Q2W, 75 mg BFKB8488A Q2W, 100 mg BFKB8488A Q2W, or placebo; [redacted].

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study with the exception of the site-designated unblinded staff who will prepare the syringes. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group

responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and IMC members.

While PK and immunogenicity samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all patients. Postbaseline immunogenicity samples from patients assigned to the comparator arm will not be analyzed for ADAs except by request.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which subject management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations. Once the treatment code is broken, the investigator should contact the Medical Monitor.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to subject unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are BFKB8488A and placebo.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 BFKB8488A and Placebo

BFKB8488A and placebo will be supplied by the Sponsor as sterile liquid in 2-mL Type I, colorless, borosilicate glass vials. For information on the formulation and handling of BFKB8488A, see the pharmacy manual and BFKB8488A Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.

[redacted]

4.3.2.1 BFKB8488A and Placebo

BFKB8488A or placebo will be administered subcutaneously, preferably in the thigh, using syringes provided to the study site. [redacted] IMP will be administered by a healthcare professional with a physician available at the time of administration. *IMP will be administered at the clinical site, and at* applicable sites. [redacted] Study drug will be administered according to the dosing schedule in the schedule of activities [redacted].

Refer to the pharmacy manual for additional details on the study drug administration.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (BFKB8488A and placebo) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate

documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to BFKB8488A

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Genentech IMP BFKB8488A or any other study treatments to patients who have completed the study. The Sponsor may evaluate whether to continue providing BFKB8488A in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, topical medications, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug until 6 weeks after the final dose of study drug. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients may continue on stable regimens of drugs they are receiving as treatment for coexistent stable diseases (e.g., antihypertensives, cholesterol-lowering drugs, or bronchodilators) unless listed as prohibited therapy (Section 4.4.2). In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice.

- Concomitant treatment with any of the following anti-diabetic medications is permitted if the dose has been stable for at least 3 months prior to randomization or since liver biopsy, whichever is longer:
  - Metformin
  - Sulfonylureas
  - Dipeptidyl peptidase-4 inhibitors
  - Insulin
  - Sodium-glucose transport protein 2 inhibitors
- Concomitant treatment with GLP-1 receptor agonists is permitted if the dose has been stable for at least 3 months prior to randomization or since liver biopsy, whichever is longer.

- [redacted]
- The use of common stable therapies for chronic primary hypertension, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta blockers, and hydrochlorothiazide, is permitted to continue assuming potassium is within normal limits.
- The continuing use of lipid-lowering therapies including statins, ezetimibe, and fibrates is permitted.
- Oral contraceptives are allowed for women of childbearing age to maintain adequate contraception.
- A mild sedative or anti-anxiety medication (e.g., benzodiazepines) may be prescribed to manage general anxiety or anxiety related to the MRI procedure.
- [redacted]
- Anti-depressant medications prescribed for stable depression is permitted.
- Acetaminophen may be used at doses of ≤1000 mg/day
- Ibuprofen may be used at doses of ≤800 mg/day.
- Medications for gastroesophageal reflux disease and asthma (except oral steroids) and mild sedatives used as sleep aids may also be continued during the study.
- [redacted]
- [redacted]

It is recommended that patients avoid changing any non-prescription drugs or vitamins within 21 days prior to randomization and during the study. During the course of the study, changes to permitted medicines for clinical reasons and therapeutic interchange for cost-effectiveness for the patient are allowed as determined by the investigator *or treating physician*. The rationale for an immediate change must be documented in the source documents and Case Report Form (CRF) as applicable. If possible, changes should be avoided until at least the end of the dosing period. Any changes regarding concomitant medications should be recorded on the patient's source documents and the CRF along with the reason for the change. Throughout the study, concomitant medications or treatments deemed necessary to provide adequate supportive care *may be prescribed* except for those listed in Section 4.4.2.

4.4.2 Prohibited Therapy

The following medications should not be taken within window as described below and throughout the duration of the study (unless the study treatment has been discontinued):

- Treatment with thiazolidinediones (e.g., pioglitazone)
- Any treatment for *hyperthyroidism*
- Oral or intravenous bisphosphonate
- Intravenous fluoride or strontium
- PTH or PTH derivatives (e.g., teriparatide, abaloparatide)
- Denosumab
- Any SERMs (e.g., tamoxifen, raloxifene, and toremifene)
- Tibolone
- Anabolic steroids or testosterone
- Systemic hormone replacement therapy *(except for thyroid hormone)*
- Calcitonin
- Active Vitamin D analogs (e.g., calcitriol, tacalcitol, paricalcitol, doxercalciferol)
- Other bone active drugs including anti-convulsants (e.g., phenytoin, carbamazepine, valproate, primidone, and phenobarbital) (except benzodiazepines) and heparin
- Systemic glucocorticoids *([redacted]*, chronic systemic ketoconazole, androgens, ACTH, cinacalcet, aluminum, lithium, protease inhibitors, gonadotropin-releasing hormone agonists.
- Calcineurin inhibitors
- Investigational therapy within 30 days or within 5 half-lives of the investigational product, whichever is longer, prior to *randomization*
- Any biological therapy within 90 days or within 5 half-lives of the biological product, whichever is longer, prior to *randomization*
- Treatment with live, attenuated vaccine within 14 days prior to randomization, during study treatment, or within 6 weeks after the final dose of BFKB8488A, unless specifically reviewed and approved by the investigator.

4.4.3 Additional Restrictions

- No food or fluids*, with the exception of water,* will be allowed for at least 8 hours prior to all study visits collecting fasting laboratory samples until after study laboratory samples are obtained. Patients should be appropriately instructed to hold medications as needed until they are able to eat.
- No food or fluids*, with the exception of water,* will be allowed for at least 4 hours prior to all MRI scans and FibroScan®. Patients should be appropriately instructed to hold medications as needed until they are able to eat.
- From screening until completion of the study, patients will abstain from significant alcohol consumption (defined as the lower of the following: local guidelines [e.g.,

2015–2020 Dietary Guidelines for Americans, 8th Edition], or AASLD Diagnosis and Management of NAFLD Practice Guidance of >21 standard drinks per week in men and >14 standard drinks per week in women, on average [Chalasani et al. 2018]), and smoke no more than 1 pack of cigarettes per day. Patients must agree to completely abstain from alcohol consumption 12 hours prior to every screening and study visit.

- Patients are advised to refrain from strenuous exercise that is unusual for them or that they are not accustomed to performing (e.g., heavy lifting, construction activity, competitive sports, running other than light jogging and aerobics) for the duration of the study. Walking at a normal pace, light jogging, and similar activities will be permitted. Patients can otherwise maintain their normal level of physical activity throughout the entire study but should not begin a new exercise program.
- Additionally, patients should refrain from donating blood during the study and for 90 days after the last dose of study drug.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in [redacted]. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

[redacted]

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history, reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional by the patient within 7 days prior to initiation of study treatment, and any medication listed as exclusion criteria in Section 4.1.2 used by a patient from 1 year prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity is recorded because of the potential contribution of this variable to differences in observed pharmacokinetics, pharmacodynamics, toxicity, and/or response to treatment.

4.5.3 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat *as well as* the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. [redacted] Height will be recorded at screening only. Weight will be measured at specified visits (see [redacted]). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and temperature. *All vitals are to be obtained prior to other procedures, except ECG, scheduled at the same visit (e.g., blood draws).* Triplicate blood pressure measures should be collected at all visits. Sites should be adequately trained to minimize variability and ensure accuracy of blood pressure measurements as recommended by published guidance (Muntner et al. 2019). [redacted]

[redacted]

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 FibroScan®

Liver stiffness will be assessed by FibroScan® at screening and additional specified visits. Study FibroScan® assessments will be conducted according to a standardized protocol described in a technical FibroScan® manual, which will be provided to all sites.

[redacted] FibroScan® results should include the probe used, the stiffness measurement, and CAP.

4.5.6 Ultrasound

An ultrasound will be conducted in all patients to screen for cholelithiasis at screening as well as at the end of the study. Local standard-of-care radiology criteria may be used for determination. If patients have had a cholecystectomy, the ultrasounds are not required.

4.5.7 Bone Mineral Density

Bone mineral density will be measured by acquiring DXA scans from all patients. Site personnel should complete training for the DXA prior to performing scans, to ensure consistent acquisition parameters and patient positioning. De-identified digital DXA results (in manufacturer's format) should be transferred to the Sponsor and/or independent review facility (IRF) for central assessment. Any patients enrolled in the study who do not meet manufacturer recommendations for body size or weight will not have a DXA performed.

4.5.8 Magnetic Resonance Imaging

All MRI exams must include measurement of liver lipid fraction using a multi-echo (e.g., ≥6) PDFF acquisition. Additional exploratory measurements, such as T1 measurement acquisitions (to assess liver fibrosis), and body composition acquisitions should be made at sites with these capabilities. Study MRI exams will be conducted according to a standardized MRI scanning protocol described in a technical MRI scanning manual, which will be provided to all sites. Site personnel should complete training for the MRI prior to performing scans, to ensure consistent acquisition parameters and patient positioning. MRI images will be transferred in digital format to an

IRF and/or to the Sponsor, as described in the MRI scanning manual, for central assessment.

4.5.9 Liver Biopsy

Biopsy specimens will be assessed at baseline and at the end of treatment (see [redacted]). An archival liver biopsy collected no more than 6 months prior to randomization, or a biopsy collected during screening may be used as the baseline. The archival biopsy must be performed while the patient is not on any treatment prescribed for the purpose of this study or on any investigational therapy for the treatment of NASH. The method of biopsy collection should include approaches to lessen the effect of regional variability or sampling error. Additional details on the liver biopsy collection and storage will be provided in a separate biopsy manual.

4.5.10 Histological Scoring Systems

Histological outcome will be assessed by the pathologist through the NAS and NASH CRN fibrosis stage.

4.5.10.1 NAFLD Activity Score

The NAS will be assessed at screening and at end-of-treatment.

NAS is a system of histologic evaluation that includes the disease spectrum from NAFLD to NASH. NAS assesses three types of lesions that comprise-grade steatosis, lobular inflammation, and ballooning (Kleiner et al. 2005). The aggregate NAS is the unweighted sum of the scores of each component of the NAS (steatosis [0–3], lobular inflammation [0–3], ballooning [0–2]).

4.5.10.2 NASH Clinical Research Network (CRN) Fibrosis Stage

The NASH CRN fibrosis stage will be assessed at screening and at end-of-treatment.

Fibrosis stage ranges from 0–4, with higher stages indicating more severe fibrosis (Kleiner et al. 2005). Fibrosis scores for Stage 1 are subdivided to distinguish between mild (1A) and moderate (1B) Zone 3, perisinusoidal fibrosis, and portal/ periportal fibrosis (Stage 1C). Stage 2 is perisinusoidal and portal/periportal fibrosis, Stage 3 is bridging fibrosis, and Stage 4 is cirrhosis.

4.5.11 Home Glucose Monitoring (Type 2 Diabetes Mellitus Patients Only)

A glucose monitor with supplies (including lancets, test strips, and control solution) will be provided to all patients with T2DM along with proper training in the use of all equipment to monitor blood glucose levels at home. The investigator should counsel patients on the signs and symptoms of hypoglycemia, how to treat the hypoglycemia, and when to contact medical personnel. *Starting after the Week 0 visit, any* blood glucose level $\leq$54 mg/dL or $\geq$270 mg/dL should be specifically logged as well as any symptoms of hypoglycemia experienced. The investigator should evaluate all reported

episodes of hypoglycemia or hyperglycemia to determine the clinical significance and the appropriate follow up.

Patients who are not taking insulin therapy should be instructed to measure and log fasting blood glucose levels at least twice weekly or if they experience any symptoms of hypoglycemia.

Patients on basal insulin should have at a minimum three-times weekly fasting measurements or if they experience any symptoms of hypoglycemia. Patients on regimens with basal and prandial insulin should additionally have fasting, pre-prandial, post-prandial, and before-bedtime measurements.

4.5.12 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis unless alternative instructions are provided:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, LDH, gamma-glutamyl transferase (GGT), and pre-albumin
- Coagulation: INR, aPTT, and PT
- Thyroid function testing: thyroid-stimulating hormone (TSH) and free thyroxine (T4) (if abnormal, repeat testing for confirmation)
- IGF-1 (if abnormal, repeat testing for confirmation)
- Blood alcohol level

- Viral serology
  - HIV antibody
  - HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) reflex HBV DNA

    If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
  - HCV serology: HCV antibody and (if HCV antibody test is positive) reflex HCV RNA

    If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- HbA_{1C}
- Fasting insulin
- Fasting lipids: cholesterol, LDL cholesterol, HDL cholesterol, very low-density lipoprotein (VLDL), and triglycerides
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed locally at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (performed *by a central or local laboratory*).
- FSH to confirm postmenopausal state in women without menses for 12 or more months without an alternative medical cause
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and reflex microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) for abnormal urine dipsticks, and urine drug test (at screening)
- 24-hour urine including cortisol and creatinine (reflex testing within 2 week if 24-hour urinary cortisol $> 1.5 \times$ ULN and $> 2 \times$ baseline)
- ACTH
- 25-hydroxy vitamin D

  If patient has vitamin D <20 ng/mL at screening, high-dose vitamin D (e.g., 50,000 IU weekly $\times$ 6 weeks) must be initiated prior to randomization, and vitamin D Institute of Medicine 2011 recommendations (800–2000 IU/Day) should be followed throughout the study.

  If Week 36 vitamin D level is <20 ng/mL, replenishment must be repeated.
- PTH
- Bone serum biomarkers (CTX and P1NP)
- Serum samples for PK analysis

- Serum samples for immunogenicity analysis
- Blood (plasma and serum) samples for exploratory research on candidate biomarkers
- Stool samples for exploratory research on the microbiota
- Archival or newly collected liver tissue sample obtained at baseline for determination of patient eligibility and for exploratory research on biomarkers
- Liver tissue sample obtained at end of treatment, if deemed clinically feasible, for determination of response to study treatment and exploratory research on biomarkers

In some cases, safety-related decisions, and interventions, e.g., close observation, may be made on the basis of local laboratory test results, before central lab results are available.

Exploratory biomarker research may include, but will not be limited to, adipokines, cleaved CK18, lipids, biomarkers of fibrosis and MRI-related imaging markers. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes. Genomic research will be aimed at exploring inherited characteristics. NGS methods may include WGS or WES of blood samples, but only at participating sites (see Section 4.5.15)

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.16), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Whole blood, plasma, serum, liver tissue, urine and stool samples collected for exploratory biomarker research will be destroyed no later than 10 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be patient to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.13 Electrocardiograms

ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see [redacted]). ECGs acquired on different days should be as closely time-matched as feasible. Single ECG recordings may be additionally obtained at unscheduled timepoints as indicated.

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should be obtained around the same time after any meal, preferably after a minimum of 3 hours. Circumstances that may induce changes in heart rate, should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular post-dose timepoint the mean QTcF is $>$500 ms and/or 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.6.1. The investigator

should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.14 Clinical Outcome Assessments

Patient-reported outcome (PRO) instruments will be completed to assess the treatment benefit and more fully characterize the safety profile of BFKB8488A. In addition, PRO instruments will enable the capture of each patient's direct experience with BFKB8488A.

PRO data will be collected through use of the following instruments: The Columbia-Suicide Severity Rating Scale (C-SSRS), the Patient Health Questionnaire-9 (PHQ-9), and the Appetite Sensations Visual Analogue Scale (VAS).

The C-SSRS is a tool used to assess the lifetime suicidality of a patient as well as any new instances of suicidality. The electronic self-rated version of the C-SSRS will be used to assess suicidal ideation and behavior (SIB) at baseline and monitor for changes in SIB at subsequent visits. For positive scores, the investigator will be alerted and should follow up with the patient to provide the appropriate intervention as soon as possible.

The PHQ-9 will be administered for monitoring of potential depression throughout the study. The PHQ-9 is a self-administered diagnostic instrument that scores each of the 9 Diagnostic and Statistical Manual of Mental Disorders criteria of depression. Following study of construct and criterion validity, the PHQ-9 has been shown as a reliable and valid measure of depression severity (Kroenke et al. 2001).

The Appetite Sensations VAS (see Appendix 2) consists of eight items with words anchored at each end expressing the most positive and the most negative rating of hunger, satiety, fullness, prospective food consumption, desire to eat something fatty, salty, sweet, or savory. This scale has reproducibility, power, and validity (Flint et al. 2000). The scales have been used with both immediate ("Right Now") and retrospective ("Past Week") recall periods (Womble et al. 2003) and have demonstrated sensitivity to effects of lorcaserin on prospective food consumption (Martin et al. 2011).

PRO instruments will be self-administered at the clinic at specified timepoints during the study [redacted], instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be pre-programmed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing

the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.15 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.15) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger

dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Refer to Section 4.5.12 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.16 Optional Samples for Research Biosample Repository

4.5.16.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for [redacted] drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.16.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.16) will not be applicable at that site.

4.5.16.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to BFKB8488A, diseases, or drug safety:

- Leftover blood, serum, plasma, urine, stool, and liver tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.16.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.16.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.16.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.16.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Any adverse event CTCAE Grade 4 or higher, regardless of attribution to study drug
- Positively detected suicidal ideation type 4 or 5 or suicidal behavior
- 24-hour urinary cortisol $> 1.5 \times$ ULN and $> 2 \times$ baseline, if confirmed on follow up visit within 2 weeks.
- If any signs or symptoms of hyper- or hypothyroidism that accompany changes in thyroid function tests (TSH or free T4) that are confirmed by repeat testing.
- Abnormal IGF-1 that is confirmed by repeat testing.
- Nontraumatic bone fracture

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced. Patients who discontinue treatment prior to study treatment completion will participate in the end-of-treatment visit at the time of early discontinuation and will enter a follow-up period for a total of 6 weeks.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. Patients in the fixed dose cohorts who withdraw from the study will not be replaced unless the IMC elects to change the dose, see Section 3.1.2. Patients in the [redacted] may be replaced as determined by the IMC, see Section 3.1.2. Patients who discontinue from the study will participate in the end-of-treatment visit at the time of discontinuation.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

BFKB8488A is not approved, and clinical development is ongoing.

The safety plan for patients in this study is based on clinical experience with BFKB8488A in completed and ongoing studies. The anticipated important safety risks for BFKB8488A are outlined below. Please refer to the BFKB8488A Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification, treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with BFKB8488A

[redacted]. For a detailed description of all the risks, please refer to the Investigator's Brochure. The risks described below include those that require additional monitoring and specific intervention.

5.1.1.1 Gastrointestinal Effects

Mild to moderate GI adverse events, namely nausea, vomiting, and diarrhea have been observed in the highest dose cohorts of the Phase Ia Study GC29819. Nausea, vomiting, and diarrhea were self-limited in all cases up to the 342 mg SC dose; however, at 681 mg SC, 6 out of 8 patients in the cohort reported adverse events of mild to moderate nausea. Four of the patients required medical intervention including intravenous fluids, ondansetron, metoclopramide, and/or loperamide. [redacted] However, GI adverse events were lower in frequency and severity, and better tolerated at the other doses including those proposed in this study.

Patients should be closely monitored for GI adverse events and early intervention is recommended. Patients should be treated as necessary according to standard of care (see Table 1).

5.1.1.2 Injection Site Reaction/Allergic or Anaphylactic Reactions to BFKB8488A

Monoclonal antibodies such as BFKB8488A may be associated with localized reactions at the site of injection. Systemic injection-related reactions as well as allergic or anaphylactic reactions could possibly also occur. These reactions can be severe or even life threatening.

Patients will be monitored for these types of reactions during and after receiving BFKB8488A and treated as per institutional guidelines. Study personnel will monitor for any injection-site reactions (per criteria in Appendix 4) or drug-related toxicities such as anaphylactic and other hypersensitivity reactions after receiving BFKB8488A*, including assessing vital signs as clinically indicated*.

5.1.1.3 Loss of Lean Body Mass or Bone Mineral Density Related to Weight Loss

[redacted] In the dose ranging Phase Ib multiple-dose study in humans, there was no significant difference overall between the BFKB8488A- and placebo-treated patients. [redacted]

[redacted]

[redacted] Additional tests may be done if clinically indicated. Reported fractures will be closely monitored by

the Sponsor for non-traumatic causes. Patients will be provided guidance regarding the recommended daily allowance for vitamin D and calcium per the Institute of Medicine 2011 recommendation.

5.1.1.4 Effect on Hypothalamic-Pituitary Axis

Because there are reports of increased corticosterone production in FGF21 transgenic mice, an important safety consideration is the potential for impact on the hypothalamic-pituitary- adrenal (HPA) axis. BFKB8488A given once intraperitoneally at 25 mg/kg induced a very modest increase in plasma corticosterone in lean chow-fed C57BL/6 mice; however, a similar drug-related response was not observed in diet-induced obese mice. [redacted]

The exclusion criteria are designed to exclude patients with abnormalities in thyroid function test at screening (including subclinical disease, as well as patients being treated for *hyperthyroidism and patients being treated for* hypothyroidism *who are not on stable treatment*), any form of Cushing's syndrome (including pituitary Cushing's disease, known adrenal insufficiency by clinical history, or patients taking systemic glucocorticoid at baseline), growth hormone deficiency, or acromegaly.

Hypothalamic-pituitary axis function will be monitored by evaluating changes in free T4, TSH, IGF-1, ACTH, and 24-hour urinary cortisol and creatinine in this study. Additional specific tests of pituitary function may be performed at the discretion of the investigator or Sponsor on the basis of emerging safety data during the course of this study.

5.1.1.5 Sympathetic Effects

[redacted] There were no meaningful changes from baseline in mean body temperature, and no adverse events of fever were reported.

The patients' vital signs including heart rate, blood pressure, and temperature will be monitored closely throughout the study, including triplicate measurements of blood

pressure. Marked hypertension as defined by a systolic blood pressure ≥180 mmHg that is at least 20 mmHg higher than the baseline measurement will be considered an adverse event of special interest, immediately reportable to the Sponsor (see Section 5.2.3).

5.1.1.6 Hypoglycemia

In murine models, BFKB8488A induced antibody-mediated activation of FGFR1/KLB complex and improvements in obesity-associated metabolic derangements including hyperglycemia (Kolumam et al. 2015). [redacted]

Patients will be monitored for signs and symptoms of hypoglycemia and have blood glucose measured at baseline and throughout study. Patients with T2DM will also be provided with a home glucose monitor, supplies, and training to monitor their fasting blood glucose levels at least twice weekly or if they experience any symptoms of hypoglycemia. Patients taking insulin will have more frequent home glucose monitoring as instructed in Section 4.5.11.

5.1.1.7 CNS Effects

[redacted] Additionally, to assess the potential CNS effects, mood, suicidal ideation and behavior will be assessed in the study for the duration of this trial by administration of the C-SSRS every 2 weeks. Prospective scales that monitor depression such as the PHQ-9 will also be administered periodically.

5.1.1.8 Exocrine Function of Pancreas

[redacted] Patients that develop diarrhea should be monitored for steatorrhea and, if needed, for malabsorption.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

In the fixed dose arms, there will be no dose modifications (dose reductions) for BFKB8488A or placebo in this study due to adverse events in individual patients. [redacted]

[redacted]

5.1.2.2 Treatment Interruption

BFKB8488A treatment may be temporarily suspended in patients who experience a treatment-emergent adverse event considered to be related to study drug. If the event improves to Grade 1 or better, treatment will resume at the next scheduled dose. If one or more scheduled dose is missed because of an ongoing adverse event, the study treatment may be restarted based on the investigator's judgment. Study treatment may be suspended for reasons other than a treatment-emergent adverse event (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.1.2.3 Management Guidelines

Toxicities associated or possibly associated with study treatment should be managed according to the management guidelines provided in this protocol or, if not specifically mentioned, according to standard medical practice.

In general, events of Grade 1 and 2 severity as per the Common Terminology Criteria for Adverse Events (CTCAE) scale should be treated symptomatically if needed while continuing the use of BFKB8488A. Study drug must be interrupted in instances of CTCAE Grade 3 adverse events related to study drug, and discontinued if they do not resolve to Grade 1 with symptomatic treatment or standard of care, or recur following resumption of dosing. All cases of CTCAE Grade 4 regardless of attribution require study drug discontinuation. A detailed list of adverse events and laboratory abnormalities necessitating study treatment discontinuation is included in Section 4.6.1.

Guidelines for management of specific adverse events are outlined in Table 1.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Nausea and vomiting	
Grade 1 or 2	• Treat with antiemetics as per local standard of care. • Provide fluid and electrolyte replacement if necessary. • If nausea occurs for less than 7 consecutive days, continue study drug. • If nausea occurs for more than 7 consecutive days, hold study drug until nausea reaches Grade 1 or resolves and then resume study drug. • [redacted]
Grade 3	• Withhold study drug. • Provide supportive treatment as per local standard of care. • After improvement to Grade 1 or resolution of symptoms and consultation with the Medical Monitor, resume study drug • [redacted]
Grade 4	• Discontinue study drug. • Treat per local standard of care.
Diarrhea	
Grade 1 or 2	• Continue study drug. • Treat with antidiarrheal agents as per local standard of care. • Provide fluid and electrolyte replacement if necessary • Evaluate for steatorrhea and, if needed, for malabsorption and treat as per local standard of care.
Grade 3	• Withhold study drug. • Provide supportive treatment as per local standard of care. • Evaluate for steatorrhea and malabsorption and treat as per local standard of care. • If the event improves to Grade 1 or less prior to the next scheduled dose, study drug may be resumed after discussion with the Medical Monitor.
Grade 4	• Discontinue study drug. • Treat per local standard of care.

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Hypertension	
Grade 1	• Continue study drug. • If >20 mm Hg increases on 2 visits, consider starting anti-hypertensive medication.
Grade 2	• Continue study drug. • Increase or start anti-hypertensive medication as per local standard of care. • Closely monitor blood pressure.
Grade 3	• Withhold study drug. • Manage marked acute hypertension as per institutional guidelines. • If the event improves to Grade 1 or less prior to the next scheduled dose, study drug may be resumed after discussion with the Medical Monitor.
Grade 4	• Discontinue study drug. • Treat per local standard of care.
Increased Liver Enzymes	
In patients with BLM of ALT and AST $<1.5\times$ ULN: If ALT or AST $>3\times$ ULN or TBL $>1.5\times$ BLM OR **In patients with BLM of ALT or AST $>1.5\times$ ULN:** If AST or ALT $>2\times$ BLM or TBL $>1.5\times$ BLM	• Repeat testing of ALT, AST, ALP and TBL within 48–72 hours, with inquiry about symptoms. If repeat testing above confirms initial result: • Repeat ALT, AST, ALP, and TBL two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic. • Obtain a more detailed history of symptoms and prior or concurrent diseases. • Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets. • Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease. • Obtain a history of exposure to environmental chemical agents. • Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin). • Consider gastroenterology or hepatology consultations. • Consider liver biopsy

Table 1 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Increased Liver Enzymes (cont.)	
In patients with BLM of ALT and AST $<2\times$ULN: If ALT or AST increases to $>5\times$ BLM	• Interrupt or discontinue BFKB8488A.
In patients with BLM of ALT and AST $\geq 2\times$ULN but $<5\times$ULN: If ALT or AST increases to $>3\times$ BLM	• Interrupt or discontinue BFKB8488A.
In patients with BLM of ALT and AST $\geq 5\times$ULN: If ALT or AST increases to $>2\times$ BLM	• Interrupt or discontinue BFKB8488A.
In patients with BLM in normal range or ALT or AST $<1.5\times$ULN: If ALT or AST increases to $>3\times$ULN accompanied by: • a concomitant increase in TBL to $>2\times$ULN OR • the INR concomitantly increases by >0.2 in any patients with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$)	• Interrupt or discontinue BFKB8488A.
In patients with BLM of ALT or AST $>1.5\times$ ULN: If ALT or AST increases to $>2\times$ BLM accompanied by: • a concomitant increase in TBL to $>2\times$ BLM OR • the INR concomitantly increases by >0.2 in any patients with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$)	• Interrupt or discontinue BFKB8488A.
• In all the above instances, continue monitoring the liver enzymes. If the levels of liver enzymes return to baseline levels, or alternate causes are clearly identified, resumption of dosing may be considered in some cases after discussion with the Medical Monitor.	

BLM = baseline measurement; INR = International Normalized Ratio; TBL = total bilirubin; ULN = upper limit of normal.

5.1.2.4 Injection-Site Reaction/Allergic and Anaphylactic Reactions

Local injection site reactions, will be treated as per local or institutional standard operating procedures. The severity of local reaction, including pain, erythema, tenderness, itching, induration, ulceration, necrosis, etc., should be graded per FDA Guidance on Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (see Appendix 4). Additionally, maximal diameter of individual ISR, duration of symptoms and treatment if any, should be recorded (see Section 5.3.5.1 and Appendix 4).

Guidance for managing anaphylaxis is described in Appendix 5.

5.1.2.5 Loss of Bone Mineral Density Related to Weight Loss

Patients will be closely monitored for bone fractures and discontinued from treatment in the event of non-traumatic bone fractures.

5.1.2.6 Hypoglycemia

Patients will be monitored for signs and symptoms of hypoglycemia and have blood glucose measured at baseline and throughout study. In the event that a patient shows signs or symptoms of hypoglycemia, has one documented blood glucose level of $\leq$54 mg/dL, or has two documented blood glucose levels of $\geq$270 mg/dL, the investigator should use clinical judgement to implement glycemic rescue treatment consistent with the local standard of care. Patients should be advised on the management of hypoglycemia according to local standard of care, and dosage of concurrent antidiabetic medication should be adjusted as necessary. Any treatment administered as part of glycemic rescue should be documented and reported to the Medical monitor immediately (see Section 5.2.3). For patients with blood glucose levels of $\geq$270 mg/dL, continuation of the patient in the study will be determined by the Medical Monitor after discussion with the investigator.

5.1.2.7 Hypothalamic Pituitary Axis

Patients will be monitored for abnormalities in free T4, TSH, IGF-1, ACTH, 24-hour urinary cortisol, and 24-hour urinary creatinine periodically during the study. If a patient is found to have an elevated 24-hour urinary free cortisol [UFC] $>1.5\times$ ULN and $>2\times$ baseline, a repeat UFC will be performed within two weeks for confirmation. If the confirmatory test is $>1.5\times$ ULN and $>2\times$ baseline, the patient must be discontinued from BFKB8488A treatment and referred to an endocrinologist for further evaluation and treatment. BFKB8488A will also be discontinued in any patient who develops an abnormal IGF-1 levels, based on age-adjusted values for the population, during the study that is confirmed by a repeat measurement. For any patients who develop abnormalities in TSH and/or free T4 (based on reference values for the population), repeat testing to confirm the increase, followed by further evaluation by an endocrinologist needs to be done. BFKB8488A must be discontinued if any signs or symptoms of hyperthyroidism or hypothyroidism accompany the changes in TSH and/or free T4.

5.1.2.8 CNS Effects and Mood

The effects on CNS and mood will be closely monitored. If a patient has a PHQ-9 score at or above 15 (moderately severe depression), at or above 10 (moderate depression) with a score of 2 or 3 for the question “Thoughts that you would be better off dead, or thoughts of hurting yourself in some way?”, or a C-SSRS suicidal ideation type 4 or 5 or behavior, he/she would be referred for timely psychiatric evaluation and/or discontinued from treatment. Study drug should be held while awaiting psychiatric evaluation. Additional monitoring of anxiety or insomnia may be performed if needed.

5.1.2.9 Management of Increases in QT Interval

Study drug should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements $>$30 minutes apart) QTcF that is $>$500 ms and $>$60 ms longer than the baseline value
- Sustained absolute QTcF that is $>$515 ms
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of patients with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such patients. The Medical Monitor should be notified as soon as possible.

In rare circumstances, it may be acceptable to resume study drug, at a lower dose, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital

signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug

- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Marked hypertension as defined by a systolic blood pressure $\geq$180 mm of Hg that is at least 20 mm higher than the baseline measurement.
- Weight loss greater than 10% of baseline (Day 1) body weight within a 12-week period at any point in the study
- Glucose measurements, serum or home glucometer readings, $\leq$54 mg/dL
- Symptomatic hypoglycemia causing altered mental status, seizures, or requiring IV dextrose for treatment
- Increases in QT interval, unless there is a clear alternative cause for the changes
    - Sustained (at least 2 ECG measurements $>$30 minutes apart) QTcF that is $>$500 ms and/or $>$60 ms longer than the baseline value
    - Sustained absolute QTcF that is $>$515 ms

    An episode of torsades de pointes or a new ECG finding of clinical concern
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

    Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is

considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4 – 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 42 days after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: *http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm*

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 3):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 3 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of anaphylactic reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of NASH.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of NASH, "nonalcoholic steatohepatitis progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of NASH

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on histologic and imaging criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For BFKB8488A (or matching placebo), adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with BFKB8488A (or matching placebo), regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Covance Medical Monitor contact information:

Medical Monitors: [redacted], M.D.

Telephone No.: [redacted] (United States)

Telephone No.: [redacted] (ex-United States)

Alternate Medical Monitor contact information for all sites:

Medical Monitor: [redacted], M.D., Ph.D.

Telephone Nos.: [redacted]

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 42 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur $>$42 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 42 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 132 days after the final dose of study drug. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 42 days after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse

Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- BFKB8488A Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary efficacy objective for this study is to evaluate the efficacy of BFKB8488A compared with placebo on the basis of the proportion of patients with resolution of NASH and no worsening of fibrosis. The primary and secondary efficacy analyses will be based on a modified intent-to-treat (mITT) approach. All patients who received at least one dose of study drug will be included in the mITT population, with patients grouped according to the treatment assigned at randomization. Analyses will be based on the final biopsy at Week 52 or MRI-PDFF measured over the course of the study.

The final analysis of data from the study will be performed when all patients have either: (i) completed the Week 52 visit and associated liver biopsy or (ii) withdrawn from the study prior to Week 52. The data analysis plan (DAP) will be specified prior to unblinding.

6.1 DETERMINATION OF SAMPLE SIZE

[redacted] will be enrolled in *two cohorts: 180 patients* in *the fixed dose cohort and* [redacted]. In the four *fixed dose* arms patients are randomized in 1:3:3:2 ratio among 3 *active drug* arms and a placebo *arm*, with approximately 20 patients in the 50 mg BFKB8488A Q2W arm,

approximately 60 patients in both the 75 mg BFKB8488A Q2W and 100 mg BFKB8488A Q2W arm and approximately 40 in the placebo arm. [redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, diabetes status, and important liver indicators of disease) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

Efficacy analysis will be conducted for the modified intent-to-treat population, defined as all randomly allocated patients who received at least one dose of BFKB8488A or placebo. Sensitivity analyses of additional study populations (e.g., completers, or per protocol [excluding major protocol violators]) may also be performed for the primary endpoint or key secondary endpoints and will be detailed in the DAP. Statistical tests will be conducted at the 0.05 significance level for the modified intent-to-treat (mITT) population. No multiple testing- adjustment is planned. Further details will be specified in the DAP prior to unblinding.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is resolution of NASH with no worsening of fibrosis at Week 52 as determined by histology as defined in Section 2.1.1. The primary endpoint will be compared between each of the two fixed BFKB8488A arms and the single variable dose arm of BFKB8488A against the pooled placebo arms using an appropriate method such as the Cochran-Mantel-Haenszel test statistic, stratified by the factors used at randomization. Reporting details and methodology including missing data handling will be specified in the DAP.

6.4.2 Secondary Efficacy Endpoints

Secondary endpoints for this study are as follows:

- Reduction in liver fat from baseline at Week 52 as measured by MRI-PDFF
- Improvement in NAS score by at least 2 points from baseline at Week 52
- Improvement in fibrosis of at least 1 stage from baseline with no worsening of NASH at Week 52

See Section 2.1.2 for definition of the endpoints. The secondary endpoints will be analyzed in the same fashion as the primary endpoint except MRI-PDFF which will use an appropriate method for continuous measurements.

Further details for the secondary efficacy analyses will be specified in the DAP.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all subjects who received at least one dose of study drug with subjects grouped according to treatment received. All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according CTCAE grading scale as specified in Section 5.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of subjects with at least one post-dose serum PK sample in which BFKB8488A is detectable, with subjects grouped according to treatment received.

Individual and mean serum BFKB8488A concentration data will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum) at relevant timepoints by dose level. Inter-subject variability will be evaluated.

Additional PK analyses (e.g. using a population PK approach) will be conducted as appropriate and may be reported separately.

6.7 IMMUNOGENICITY ANALYSES

Patient sample assessment for the presence of ADA are triaged by first testing in a screening assay, followed by testing screen ADA-positive samples in a confirmatory assay. Confirmed ADA-positive sample are then evaluated for the relative quantitation of ADA in a titration assay.

Patient ADA status is defined as follows:

- ADA-negative: Any patient with no post-baseline ADA-positive sample
- ADA-positive:
  - Patients with baseline ADA-negative and any post-baseline ADA-positive sample (treatment-induced);
  - Patients who are baseline ADA-positive and whose ADA titer is 4-fold greater than the baseline value (i.e., 0.6 titer units greater than baseline; treatment-enhanced).
- Treatment-emergent ADA-positive: Treatment-induced and treatment-enhanced
- Treatment-unaffected: Baseline ADA-positive with post-baseline ADA-positive titers $<$4-fold baseline (i.e., $<$0.6 titer unit increase)

Further characterization of the ADA-positive responses may be conducted based upon the initial assessment of the data, for example domain mapping of the ADA binding site.

Both baseline prevalence and post-baseline incidence of ADA-positive patients will be reported. An impact assessment of ADA on clinical endpoints of interest will be conducted. This will include the assessment of ADA impact on PK parameters, PD, safety, and efficacy endpoints. Included in this analysis will be a comparison of ADA-negative versus treatment-emergent ADA-positive patients, and potentially by ADA-positive titer subgroups. Additional analyses may be conducted based upon these results. The relationship between ADA status and safety, activity, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

Exploratory analyses will be conducted to evaluate the effect of BFKB8488A on exploratory biomarkers such as those listed in Section 2.5. Exploratory biomarkers may be analyzed before and after dosing with BFKB8488A to determine the relationship between PK exposure and exploratory biomarker levels. In addition, relationships amongst biomarkers may be assessed.

WGS data will be analyzed in the context of this study and explored in aggregate with data from other studies to increase researcher's understanding of disease pathobiology and guide the development of new therapeutic approaches.

6.9 HEALTH STATUS UTILITY ANALYSES

Change from baseline in VAS scores will be calculated at specified timepoints.

6.10 INTERIM ANALYSES

6.10.1 Planned Interim Analysis

A single planned interim analysis will be conducted when at least [redacted] of the patients in the fixed dose arms have completed the Week 16 MRI-PDFF. The interim analysis results will be reviewed. A DAP will be drafted prior to the interim, including the variables that will be assessed by treatment arm as well as a list of individuals who will be unblinded including the IMC.

6.10.2 Optional Interim Analyses

The Sponsor may choose to conduct interim efficacy analyses of select endpoints. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be reviewed by an IMC. Details of the interim will be pre-specified in the DAP prior to review by the IMC.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data, pharmacokinetic, biomarker, and imaging results will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for

Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for controlling and monitoring these risks. Risk monitoring will

include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech, Inc., a member of the Roche group, and will be managed by a contract research organization (CRO). The CRO deliverables will include but not be limited to clinical operations management, safety support, and medical monitoring support to the Sponsor.

Sites globally will participate to enroll up to [redacted]. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. An independent radiologic review facility will be used for the purpose of collecting and assessing the quality of MRI and DXA scans throughout the trial. The review facility will retain copies of scans for centralized assessments of imaging-related endpoints.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared

with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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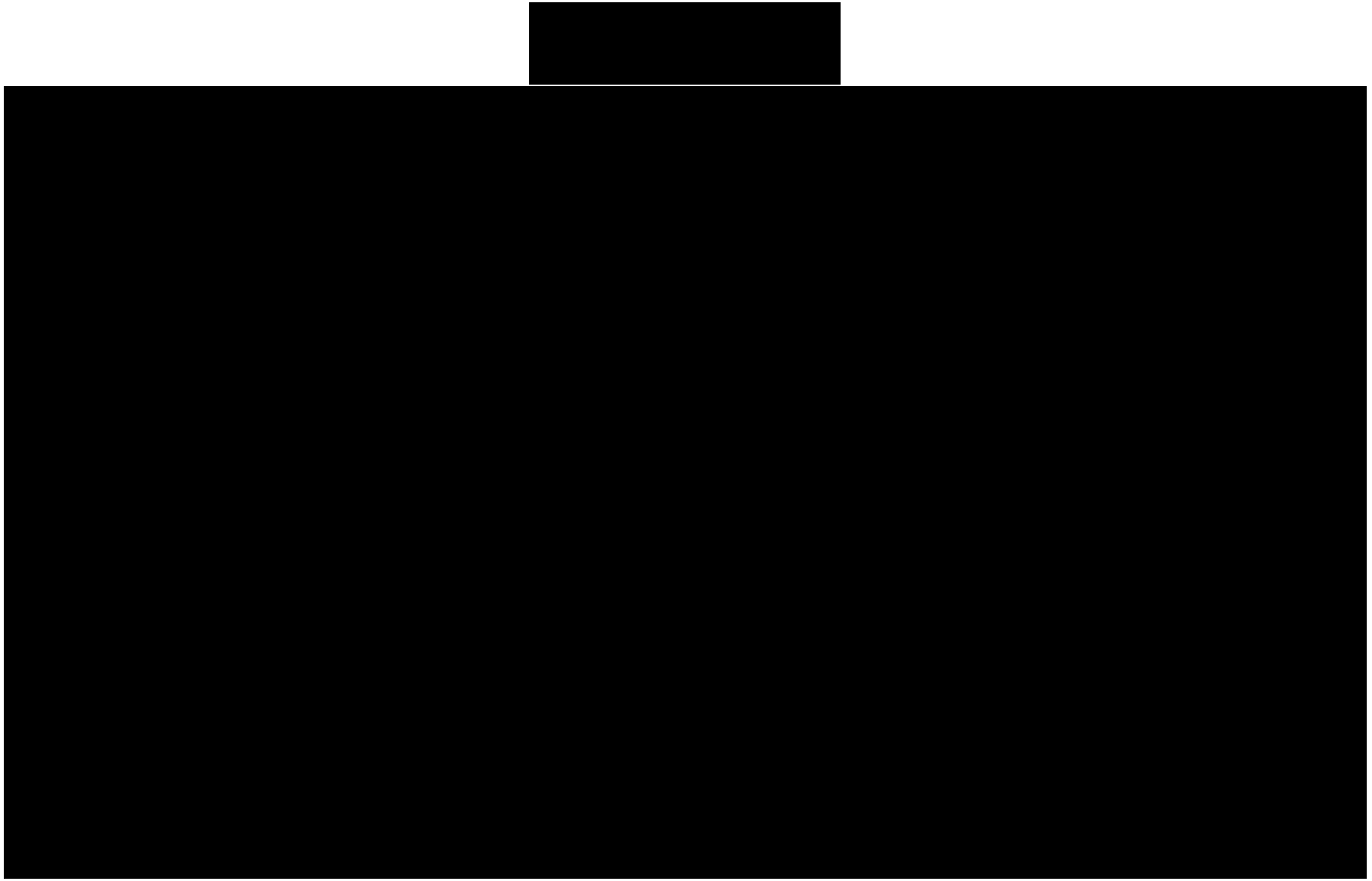

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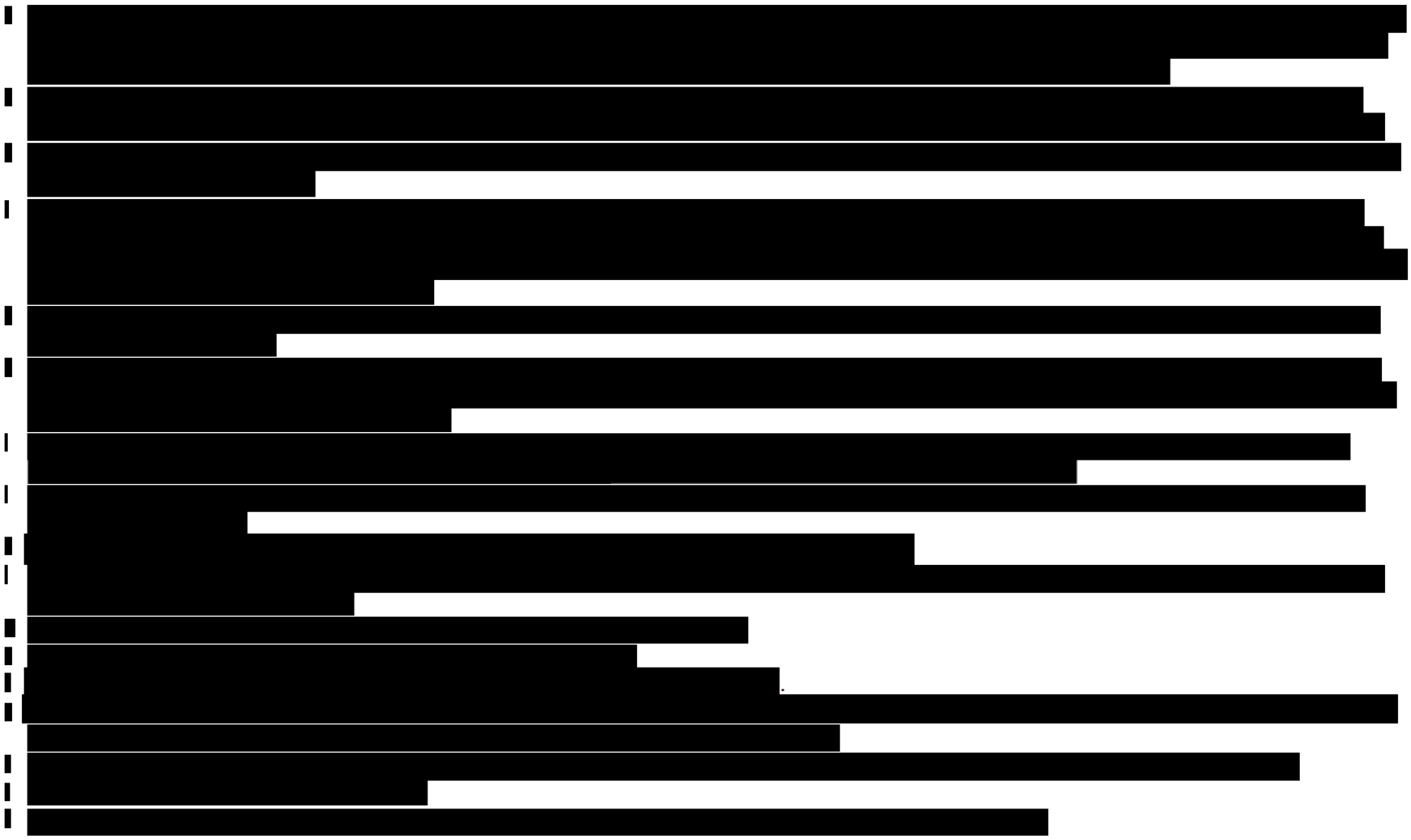

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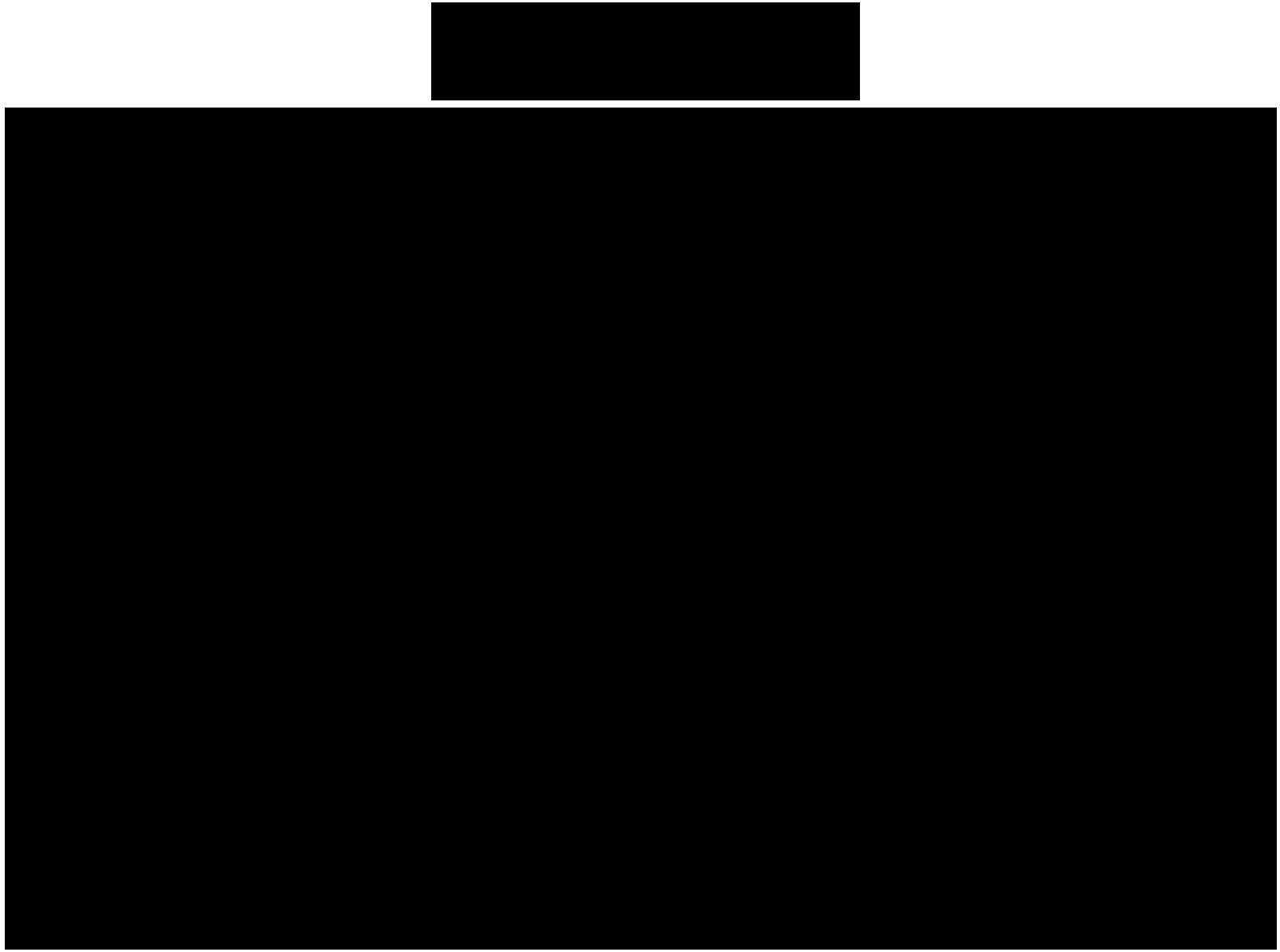
Appendix 2
Appetite Sensations Visual Analogues Scale Questionnaire

I was not hungry at all.	How hungry did you feel? _____	I had never been hungrier.
I was completely empty.	How satisfied did you feel? _____	I could not eat another bite.
Not at all full	How full did you feel? _____	Totally full
Nothing at all	How much did you think you could eat? _____	A lot
Yes, very much	Did you want to eat something sweet? _____	No, not at all
Yes, very much	Did you want to eat something salty? _____	No, not at all
Yes, very much	Did you want to eat something savory? _____	No, not at all
Yes, very much	Did you want to eat something fatty? _____	No, not at all



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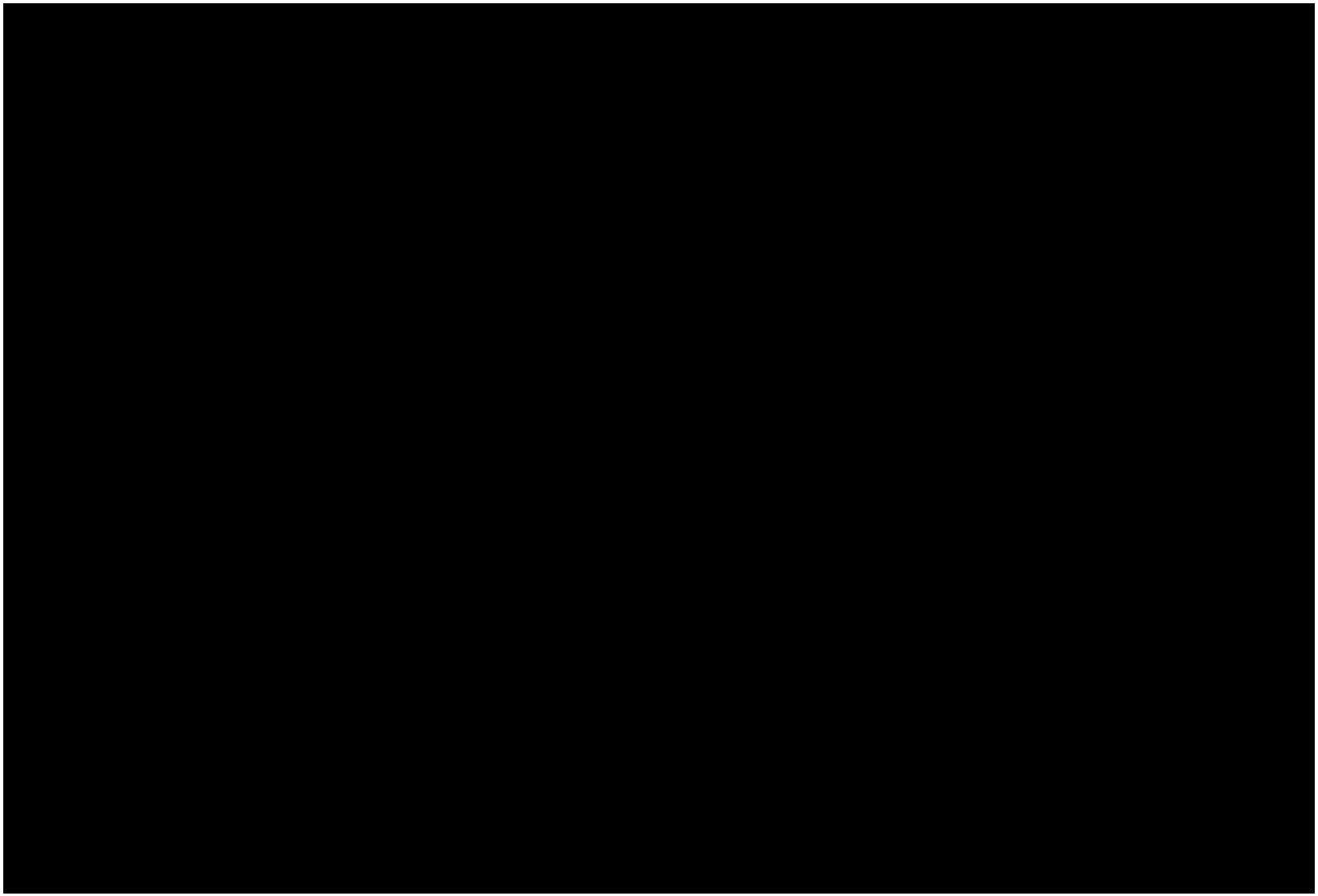

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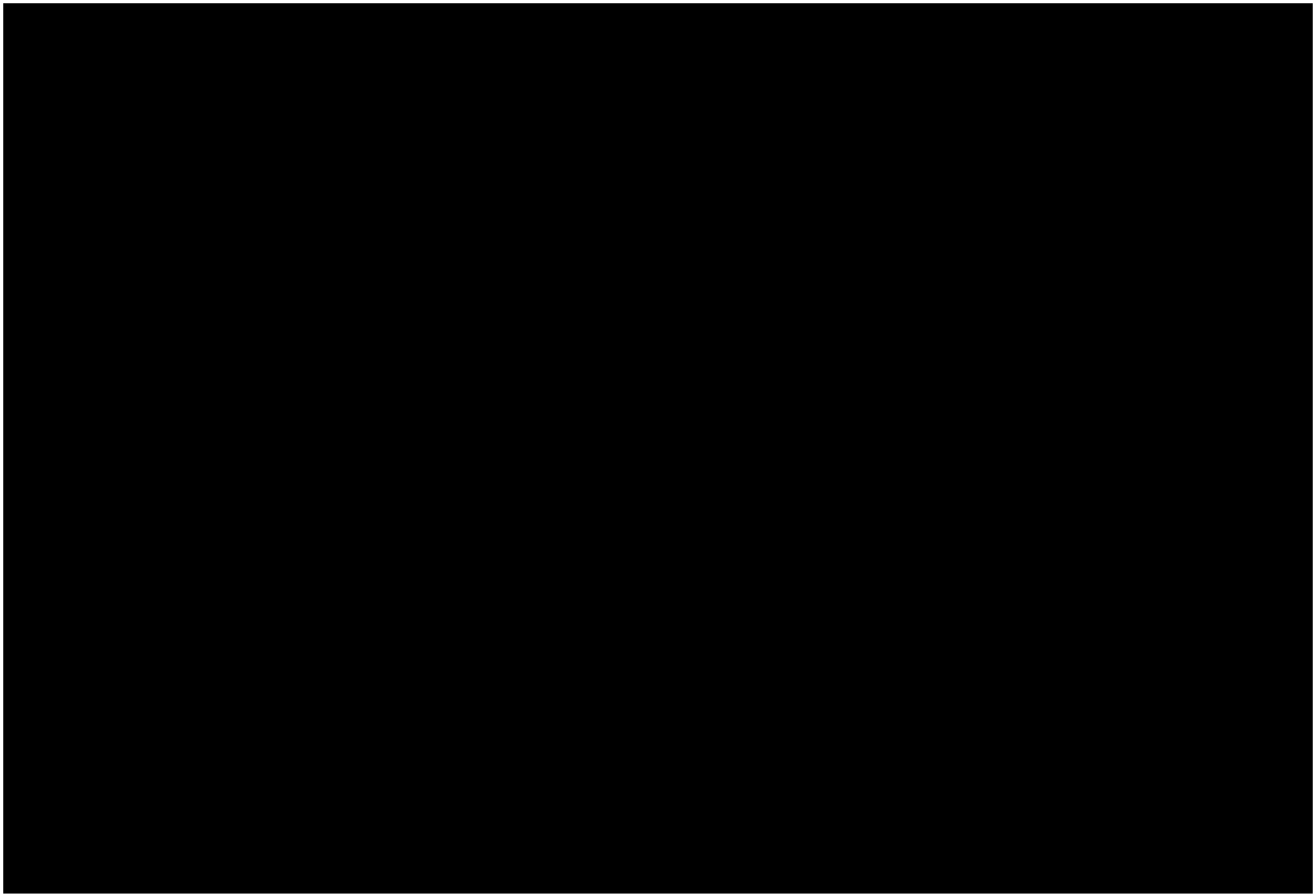

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Appendix 4
Grading of Injection Site Reactions

These guidelines are adapted from the FDA Guidance on Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, and intended as a reference for grading injection site reactions. Injection-site reactions should be treated as per pertinent local or institutional standard operating procedures.

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness [a]	2.5–5 cm	5.1–10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/swelling [b]	2.5–5 cm and does not interfere with activity	5.1–10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

ER = emergency room.

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Appendix 5
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

RECOMMENDED EQUIPMENT AND MEDICATION

The following equipment and medication are recommended in the event of a suspected anaphylactic reaction during study treatment injection in a hospital setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment injection, the following procedures are recommended:

1. Stop the study treatment injection, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.
7. Collect serum samples for immunogenicity testing.
8. Ask the patient to return for immunogenicity sample collection at the time of washout, if appropriate.