Official Title: A Phase II Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Fenebrutinib in Patients Previously Enrolled in a Fenebrutinib Chronic Spontaneous Urticaria Study

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PROTOCOL

TITLE:	**A PHASE II OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF FENEBRUTINIB IN PATIENTS PREVIOUSLY ENROLLED IN A FENEBRUTINIB CHRONIC SPONTANEOUS URTICARIA STUDY**
PROTOCOL NUMBER:	GS40868
VERSION NUMBER:	1
EUDRACT NUMBER:	2018-002296-17
IND NUMBER:	137810
TEST PRODUCT:	Fenebrutinib (GDC-0853, RO7010939)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
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FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
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PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE II OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF FENEBRUTINIB IN PATIENTS PREVIOUSLY ENROLLED IN A FENEBRUTINIB CHRONIC SPONTANEOUS URTICARIA STUDY**
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TEST PRODUCT:	Fenebrutinib (GDC-0853, RO7010939)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

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 as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF FENEBRUTINIB IN PATIENTS PREVIOUSLY ENROLLED IN A FENEBRUTINIB CHRONIC SPONTANEOUS URTICARIA STUDY**
PROTOCOL NUMBER:	GS40868
VERSION NUMBER:	1
EUDRACT NUMBER:	2018-002296-17
IND NUMBER:	137810
TEST PRODUCT:	Fenebrutinib (GDC-0853, RO7010939)
PHASE:	Phase II
INDICATION:	Chronic Spontaneous Urticaria
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This open-label extension (OLE) study will evaluate the long-term safety and efficacy of fenebrutinib in patients with chronic spontaneous urticaria (CSU). Specific objectives and corresponding endpoints for the study are outlined below.

Safety Objective

The primary safety objective for this study is to evaluate the long-term safety of fenebrutinib on the basis of the following endpoints:

- Incidence, nature, severity, and timing of adverse events, with severity characterized as either mild, moderate, or severe
- Change from parent-study baseline in targeted clinical laboratory test results at Weeks 4, 8, and 12 and at specified timepoints thereafter (approximately every 12 weeks)

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of fenebrutinib on the basis of the following endpoints:

- Change from parent study baseline in Urticaria Activity Score over 7 days (UAS7) at Weeks 4, 8, and 12
- Change from parent study baseline in Urticaria Control Test (UCT) score at Weeks 4, 8, and 12 and at specified timepoints thereafter (approximately every 12 weeks)
- Withdrawal of standard-of-care H_1-antihistamines for CSU (background therapy) summarized every 6 months
- Physician's Global Assessment of Disease Control (PhyGA) summarized at Weeks 4, 8, and 12 and at specified timepoints thereafter (approximately every 12 weeks)

Pharmacokinetic Objectives

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

- Plasma concentrations of fenebrutinib at specified timepoints

[redacted]

Study Design

Description of Study

This is a Phase II, multicenter, OLE study to evaluate the long-term safety and efficacy of fenebrutinib in patients with CSU who have completed the treatment period in a fenebrutinib CSU parent study. Patients may enroll in this OLE study at any time after completing the treatment period of the parent study.

Patients will receive open-label fenebrutinib at a dose of 200 mg orally (PO) twice a day (BID). Treatment may continue until the end of the study.

Because some patients enrolling in this study may be receiving fenebrutinib for the first time (i.e., those patients randomly assigned to placebo in the parent study), all patients will be monitored at Weeks 4, 8, and 12. Thereafter, patients will be monitored approximately every 12 weeks.

Patients should maintain a stable dose of standard-of-care H_1-antihistamines (background therapy) for the first 12 weeks of the study. Discontinuation or reduction in the dose of standard-of-care H_1-antihistamines may be attempted at any time after the first 12 weeks, at the investigator's discretion.

Number of Patients

Up to 165 patients from parent study GS39684 are expected to be enrolled globally.

Target Population

This study will enroll patients with CSU who have completed the treatment period in a fenebrutinib CSU parent study.

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Completion of the treatment period as specified in the parent study
- Acceptable demonstration of tolerance to study drug during the parent study as determined by the investigator or Medical Monitor
- For patients receiving treatment with proton-pump inhibitors (PPIs) or H_2-receptor antagonists (H_2RAs), agreement to maintain treatment at a stable dose for the first 12 weeks of the study
- 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 contraceptive methods with a failure rate of $<$1% per year during the treatment period and for at least 4 weeks after the final dose of fenebrutinib. 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 ($\geq$ 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, and copper intrauterine devices.

  Hormonal contraceptive methods containing estrogen must be supplemented by a barrier method.

  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 a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 4 weeks after the final dose of fenebrutinib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  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 preventing drug exposure.

Exclusion Criteria

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 4 weeks after the final dose of fenebrutinib

  Women of childbearing potential must have a negative urine pregnancy test result prior to initiation of the first dose of study drug.

- Treatment with any investigational agent or live/attenuated vaccine in the preceding 6 weeks

  Seasonal influenza vaccination is permitted if the inactivated vaccine formulation is administered.
- Any signs or symptoms of infection judged by the investigator to be clinically significant since completing the treatment period of the parent study
- Any significant changes (e.g., events, changes in medication) occurring after completion of participation in the parent study that, in the investigator's judgment, would increase the risk of adverse events in this OLE study

End of Study

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

Length of Study

The end of the study is expected to occur 12 months after the last patient from the parent study is enrolled in this study. The Sponsor may decide to terminate the study at any time or amend the study to extend its duration. Patients enrolled in this study may be eligible to enroll into a separate extension study, if opened.

Investigational Medicinal Products

Fenebrutinib

Patients will receive open-label fenebrutinib at a dose of 200 mg PO BID. Patients will receive the first dose of fenebrutinib at the Day 1 study visit. Thereafter, fenebrutinib will be self-administered. Each dose, administered approximately every 12 hours (i.e., twice a day, morning and evening), will consist of four 50-mg tablets (i.e. eight tablets per day).

Non-Investigational Medicinal Products

Background Therapy: Standard-of-Care H1-Antihistamines for Chronic Spontaneous Urticaria

All patients will be permitted to take H_1-antihistamine medications consistent with standard of care during the study. Patients should maintain a stable dose of standard-of-care H1-antihistamines for the first 12 weeks of the study. Discontinuation or reduction in the dose of standard-of-care H1-antihistamines may be attempted at any time after the first 12 weeks, at the investigator's discretion. If an attempt is unsuccessful, the medication may be returned to an effective dose at the discretion of the investigator. In addition, standard-of-care H1-antihistamines may be added at any time during the study, at the investigator's discretion.

Statistical Methods

Safety Analyses

The safety analysis population will consist of all patients who received at least one dose of study drug. Safety will be assessed through descriptive summaries of adverse events and laboratory test results.

Determination of Sample Size

No formal sample size calculations were performed for this OLE study.

Interim Analysis

No formal interim analysis is planned. Data cuts may be performed at appropriate timepoints for inclusion in the submission with the parent study to support evaluation of the safety profile.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
BCRP	breast cancer resistance protein
BID	twice a day
BTK	Bruton's tyrosine kinase
CIU	chronic idiopathic urticaria
ClinRO	clinician-reported outcome
CSU	chronic spontaneous urticaria
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
FcεRI	high-affinity IgE receptor
GI	gastrointestinal
H_2RA	H_2-receptor antagonist
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
MAD	multiple-ascending dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect level
OLE	open-label extension
PD	pharmacodynamic
PhyGA	Physician's Global Assessment of Disease Control
PhyGA-LS	Physician's Global Assessment of Disease Control-Likert Scale
PK	pharmacokinetic
PO	orally, by mouth
PPI	proton-pump inhibitor
PRO	patient-reported outcome
Q4W	every 4 weeks
QD	once a day
QTcF	QT interval corrected through use of Fridericia's formula
TPO	thyroperoxidase

Abbreviation	Definition
UAS	Urticaria Activity Score
UAS7	Urticaria Activity Score over 7 days
UCT	Urticaria Control Test
ULN	upper limit of normal
XLA	X-linked agammaglobulinemia

1. BACKGROUND

1.1 BACKGROUND ON CHRONIC SPONTANEOUS URTICARIA

Chronic spontaneous urticaria (CSU, also referred to as chronic idiopathic urticaria [CIU]), is defined by the presence of wheals (hives), angioedema, or both, for at least 6 weeks without an obvious cause (Greaves 2003). CSU can be a debilitating condition because of a lack of clinical response as well as the unpredictable course of the disease, both of which can have a profound negative influence on the patient's quality of life (Tilles 2005).

The etiology of CSU is not clear. Some studies have found that approximately 30%–60% of patients with CSU have an autoimmune component as evidenced by the presence of a positive autologous serum skin test (Fiebiger et al. 1995; Tong et al. 1997; Zweiman et al. 1998). One hypothesis suggests that IgE antibodies targeted against an endogenous antigen could result in the activation of skin mast cells and release of chemical mediators, such as histamine, that lead to the wheal and flare formation of a hive. In fact, recent findings in a study of more than 450 patients with CSU indicate that greater than 50% of those patients have IgE antibodies directed against thyroperoxidase (TPO) (Altrichter et al. 2011). While an autoimmune etiology can be found in a large percentage of patients, many patients do not have an identified autoimmune etiology despite having a similar disease presentation (Ferrer 2015). A common pathway in CSU is the abnormal activation of mast cells and basophils in the skin. Increased numbers of mast cells can be found in both affected and unaffected skin (Kay et al. 2014), and mast cells from patients with CSU are more sensitive, have lower thresholds for activation, and respond more robustly by releasing more histamine and other inflammatory mediators. Similarly, increased numbers of basophils have been seen in the lesional and non-lesional skin of patients with CSU (Ying et al. 2002). Collective data from several studies suggest that basophil signaling and activation are dysregulated in patients with CSU (Luquin et al. 2005).

Patients may remain symptomatic despite ongoing H_1-antihistamine treatment (up to four times the approved dose per local treatment guidelines; Powell et al. 2015), and for this group of patients, therapies such as immunosuppressants (including cyclosporine, corticosteroids, intravenous immunoglobulin G, and methotrexate) and plasmapheresis have been used (Kozel and Sabroe 2004). These agents have variable success and may be associated with severe adverse effects. More recently, omalizumab was approved for treatment of refractory CSU/CIU.

1.2 ROLE OF BRUTON'S TYROSINE KINASE

Bruton's tyrosine kinase (BTK) is essential for the differentiation and activity of B cells during immune system ontogeny and normal adaptive immune responses. BTK is important in IgE receptor (FcεRI) signaling in both basophils and mast cells, the key cell types in the pathogenesis of CSU. BTK null mice have impaired FcεRI signaling, resulting in decreased histamine and inflammatory cytokine release (Hata et al. 1998;

Iyer et al. 2011). IgE-mediated activation of mast cells and basophils via their surface FcεRI receptors results in the release of histamine and other inflammatory molecules.

1.3 BACKGROUND ON FENEBRUTINIB

Fenebrutinib (GDC-0853) is a highly selective, orally administered, reversible inhibitor of BTK that is being developed as a potential therapeutic for autoimmune diseases, including CSU.

Fenebrutinib has undergone extensive investigation in nonclinical in vitro and in vivo studies to characterize its pharmacological, metabolic, and toxicological properties.

As of 12 March 2018, fenebrutinib or placebo has been administered to 1099 subjects (i.e., 333 healthy subjects, 24 patients with hematological malignancies, 576 patients with rheumatoid arthritis, 129 patients with systemic lupus erythematosus, and 37 patients with CSU) at doses ranging from 0.5 to 600 mg. Fenebrutinib has been generally well tolerated, with no concerns leading to a change in the conduct of the studies.

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

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This open-label extension (OLE) study GS40868 is designed to assess the long-term safety and efficacy of fenebrutinib in patients with CSU. The study will enroll patients previously enrolled in Study GS39684 (parent study).

Parent study GS39684 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of fenebrutinib as add-on therapy for the treatment of adult patients with CSU aged 18–75 years who remain symptomatic despite treatment with H_1-antihistamines. The pilot cohort (Cohort 1) of Study GS39684 has been completed. On the basis of data from Cohort 1, a dose-ranging cohort (Cohort 2), has been opened. The dose regimen of fenebrutinib selected for this OLE study, 200 mg orally (PO) twice a day (BID), is the highest dose with an acceptable safety profile in Study GS39684.

Section 5.1 outlines the safety plan for potential risks associated with fenebrutinib. Refer to the Fenebrutinib Investigator's Brochure for a complete summary of safety information.

2. OBJECTIVES AND ENDPOINTS

This OLE study will evaluate the long-term safety and efficacy of fenebrutinib in patients with CSU. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 SAFETY OBJECTIVE

The primary safety objective for this study is to evaluate the long-term safety of fenebrutinib on the basis of the following endpoints:

- Incidence, nature, severity, and timing of adverse events, with severity characterized as either mild, moderate, or severe
- Change from parent-study baseline in targeted clinical laboratory test results at Weeks 4, 8, and 12 and at specified timepoints thereafter (approximately every 12 weeks)

2.2 EXPLORATORY EFFICACY OBJECTIVE

The exploratory efficacy objective for this study is to evaluate the long-term efficacy of fenebrutinib on the basis of the following endpoints:

- Change from parent study baseline in Urticaria Activity Score over 7 days (UAS7) at Weeks 4, 8, and 12
- Change from parent study baseline in Urticaria Control Test (UCT) score at Weeks 4, 8, and 12 and at specified timepoints thereafter (approximately every 12 weeks)
- Withdrawal of standard-of-care H_1-antihistamines for CSU (background therapy) summarized every 6 months
- Physician's Global Assessment of Disease Control (PhyGA) summarized at Weeks 4, 8, and 12 and at specified timepoints thereafter (approximately every 12 weeks)

2.3 PHARMACOKINETIC OBJECTIVES

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

- Plasma concentrations of fenebrutinib at specified timepoints

[redacted]

[redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase II, multicenter, OLE study to evaluate the long-term safety and efficacy of fenebrutinib in patients with CSU who have completed the treatment period in a fenebrutinib CSU parent study. Patients may enroll in this OLE study at any time after completing the treatment period of the parent study. Up to 165 patients from parent study GS39684 are expected to be enrolled globally.

Patients will receive open-label fenebrutinib at a dose of 200 mg PO BID. Treatment may continue until the end of the study (see Section 3.2).

Because some patients enrolling in this study may be receiving fenebrutinib for the first time (i.e., those patients randomly assigned to placebo in the parent study), all patients will be monitored at Weeks 4, 8, and 12. Thereafter, patients will be monitored approximately every 12 weeks (see Appendix 1).

Patients should maintain a stable dose of standard-of-care H_1-antihistamines (background therapy) for the first 12 weeks of the study. Discontinuation or reduction in the dose of standard-of-care H_1-antihistamines may be attempted at any time after the first 12 weeks, at the investigator's discretion (see Sections 4.3.2.2 and 4.4 for details on background and concomitant therapies).

Monitoring for safety and tolerability will continue throughout the study, including evaluation of clinical laboratory results and assessment of adverse events. Patients with

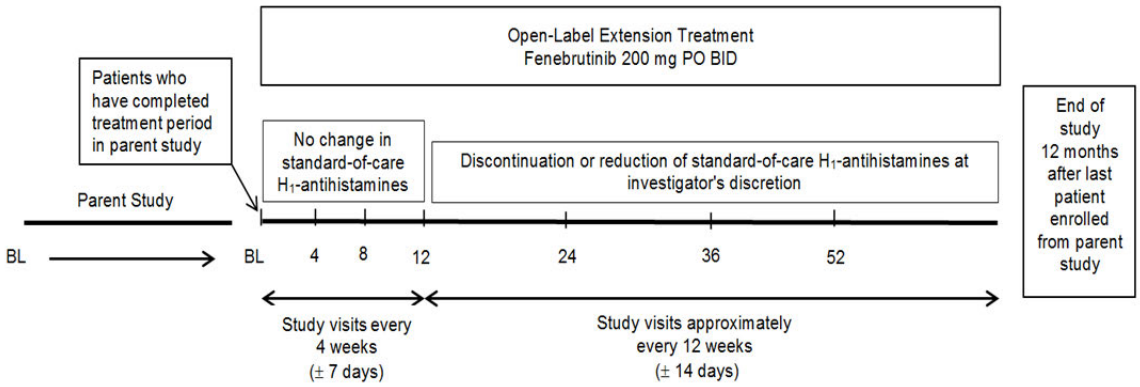
disease worsening, as determined by the investigator, should return to the clinic as soon as possible for an unscheduled visit. The investigator may also conduct an unscheduled visit to assess the patient's disease condition.

Patients who discontinue study treatment (see Sections 4.6.1 and 5.1.2.2) will be asked to return to the clinic for a safety follow-up visit approximately 4 weeks after the last dose of study drug. Patients who refuse to complete the safety follow-up period should return to the clinic for treatment discontinuation visit.

Details regarding assessments at the safety follow-up, treatment discontinuation, and unscheduled visits are provided in Appendix 1.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



BID = twice a day; BL = baseline; PO = by mouth.

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 occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 12 months after the last patient from the parent study is enrolled in this study. The Sponsor may decide to terminate the study at any time or amend the study to extend its duration. Patients enrolled in this study may be eligible to enroll into a separate extension study, if opened.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Fenebrutinib Dose and Schedule

The dose regimen of fenebrutinib 200 mg PO BID was the only dose tested in Cohort 1 of parent study GS39684.

[redacted]

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll patients with CSU who have completed the treatment period in a fenebrutinib CSU parent study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Completion of the treatment period as specified in the parent study
- Acceptable demonstration of tolerance to study drug during the parent study as determined by the investigator or Medical Monitor
- For patients receiving treatment with proton-pump inhibitors (PPIs) or H_2-receptor antagonists (H_2RAs), agreement to maintain treatment at a stable dose for the first 12 weeks of the study
- 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 contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for at least 4 weeks after the final dose of fenebrutinib. 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, and copper intrauterine devices.

Hormonal contraceptive methods containing estrogen must be supplemented by a barrier method.

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 a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 4 weeks after the final dose of fenebrutinib to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  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 preventing drug exposure.

4.1.2 Exclusion Criteria

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 4 weeks after the final dose of fenebrutinib

  Women of childbearing potential must have a negative urine pregnancy test result prior to initiation of the first dose of study drug.

- Treatment with any investigational agent or live/attenuated vaccine in the preceding 6 weeks

  Seasonal influenza vaccination is permitted if the inactivated vaccine formulation is administered.

- Any signs or symptoms of infection judged by the investigator to be clinically significant since completing the treatment period of the parent study
- Any significant changes (e.g., events, changes in medication) occurring after completion of participation in the parent study that, in the investigator's judgment, would increase the risk of adverse events in this OLE study

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

All patients in this study will have the opportunity to receive treatment with fenebrutinib at a dose of 200 mg PO BID. All patients, study site personnel, Sponsor agents, and Sponsor personnel will be unblinded to the treatment assignment of this study; however, the treatment assignment from the parent study will remain blinded until the parent study is unblinded.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is fenebrutinib.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Fenebrutinib

Fenebrutinib will be supplied by the Sponsor as 50-mg tablets. Tablets will be supplied in bottles appropriately labeled for this study. Fenebrutinib tablets should be stored at room temperature. For information on the formulation and handling of fenebrutinib, see the pharmacy manual and the Fenebrutinib Investigator's Brochure.

4.3.1.2 Background Therapy: Standard-of-Care H_1-Antihistamines for Chronic Spontaneous Urticaria

Patients should maintain a stable dose of standard-of-care H_1-antihistamines for the first 12 weeks of the study (see Section 4.3.2.2 for details). Refer to the local prescribing information for the formulation, packaging, and handling of these medications.

4.3.2 Study Treatment Dosage, Administration, and Compliance

4.3.2.1 Fenebrutinib

The treatment regimen is summarized in Section 3.1. Patients will receive the first dose of fenebrutinib at the Day 1 study visit. Thereafter, fenebrutinib will be self-administered. Each dose, administered approximately every 12 hours (i.e., twice a day, morning and evening), will consist of four 50-mg tablets (i.e. eight tablets per day). Fenebrutinib may be taken with or without food. Patients should be instructed that a missed dose should not be taken with the next scheduled dose.

Fenebrutinib tablets will be dispensed on site every 4 weeks. For periods in which study site visits (for assessments) are scheduled >4 weeks apart, patients will be expected to visit the site to receive allotment of study drug.

Sites will be responsible for pre-populating the bottle label with the dates when patients are scheduled to take study drug during that time period. Under the corresponding dates listed on the affixed label, patients will record the time (morning and evening) each dose is taken. Refer to Appendix 6 for bottle and label configuration.

To assess patient compliance with study drug administration, patients will be directed to bring all empty and partially-filled bottles to each study visit. The number of tablets issued minus the number of tablets returned will be used to calculate the number of tablets taken. Dosing compliance will be documented in the source documents. If compliance is ≤80%, the investigator or designee should counsel the patient and ensure steps are taken to improve compliance.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.4.4.

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

4.3.2.2 Background Therapy: Standard-of-Care H_1-Antihistamines for Chronic Spontaneous Urticaria

All patients will be permitted to take H_1-antihistamine medications consistent with standard of care during the study. Standard-of-care H_1-antihistamines should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients should maintain a stable dose of standard-of-care H_1-antihistamines for the first 12 weeks of the study. Discontinuation or reduction in the dose of standard-of-care H_1-antihistamines may be attempted at any time after the first 12 weeks, at the investigator's discretion. If an attempt is unsuccessful, the medication may be returned to an effective dose at the discretion of the investigator. In addition, standard-of-care H_1-antihistamines may be added at any time during the study, at the investigator's discretion. Exacerbations of urticaria may be treated with standard-of-care medications (e.g., short course of systemic corticosteroids for up to 10 days) (Zuberbier et al. 2018).

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using an interactive voice or web-based response system 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 (if supplied by 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 Fenebrutinib

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

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

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from entry into the extension study to the study completion/discontinuation visit of the extension study. All such medications, including standard-of-care H_1-antihistamines for CSU, should be reported to the investigator and recorded on the Concomitant Medications eCRF. The investigator should consult the prescribing information and contact the Medical Monitor (or delegate) if questions arise regarding concomitant medications not listed in the protocol.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Hormone-replacement therapy or oral contraceptives

  Hormone-replacement therapy or hormone contraceptives containing the CYP3A substrate ethinyl estradiol (with the concomitant use of a barrier method) is permitted. However, these agents should be used with caution as outlined in Section 4.4.2.3.

- Dietary supplements, defined as vitamins, minerals, purified food substances, and herbal therapies with pharmaceutical properties

  Vitamins, minerals, and purified food substances are permitted in amounts lower than that known to be associated with adverse effects (e.g., hypervitaminosis). Herbal therapies with pharmaceutical properties are permitted only if there is acceptable evidence of no CYP3A inhibition or induction.

- Leukotriene receptor antagonists or H_2RAs for diseases other than CSU (e.g., asthma or gastroesophageal reflux disease, respectively) at a stable dose
- PPIs or H_2RAs at a stable dose, up to the maximum recommended dose according to the local prescribing information
- Inhaled asthma controllers, including inhaled corticosteroids

4.4.2 Cautionary Therapy

Categories of medications that are to be avoided or used with caution when combined with fenebrutinib are described below, and Appendix 5 lists examples of medications within these categories. If use of one of these medications is necessary, the risks and benefits should be discussed with the Medical Monitor (or delegate) prior to concomitant administration with fenebrutinib.

4.4.2.1 Immunosuppressive Agents

Caution is advised if adding an immunosuppressive agent (e.g., methotrexate, mycophenolate mofetil, cyclophosphamide, rituximab, tacrolimus) to ongoing treatment with fenebrutinib.

4.4.2.2 Acid-Reducing Agents

Patients who use antacids for symptomatic relief of heartburn (e.g., Pepto-Bismol®, Rolaids®) should take fenebrutinib at least 2 hours before or 2 hours after antacid administration because gastric acid improves fenebrutinib absorption.

4.4.2.3 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

Preliminary data from the clinical drug–drug interaction study (GP39616), evaluating the effect of fenebrutinib on the pharmacokinetics of the sensitive CYP3A substrate midazolam, suggest that fenebrutinib can be classified as a mild inhibitor of CYP3A at clinically relevant doses. It is possible that fenebrutinib inhibition of CYP3A may alter the metabolism of CYP3A substrates and result in increased plasma concentrations of CYP3A substrates. Therefore, medications in the following categories should be used with caution and in consultation with the Medical Monitor (or delegate) as needed:

- Sensitive CYP3A substrates
- CYP3A substrates with a narrow therapeutic window

The use of hormone-replacement therapy or hormone contraceptives containing the CYP3A substrate ethinyl estradiol (with the concomitant use of a barrier method) is permitted. Ethinyl estradiol is metabolized by CYP3A (Wang et al. 2004; Zhang et al. 2007) so plasma concentrations of ethinyl estradiol are expected to increase in the presence of fenebrutinib. Ethinyl estradiol is not a sensitive substrate of CYP3A (FDA 2016). Therefore, the magnitude of increase in ethinyl estradiol plasma concentrations is expected to be less than the increase observed in midazolam concentrations (i.e., less than 2-fold) in Study GP39616. Minor increases in ethinyl

estradiol concentrations are not generally associated with adverse events (e.g., Ortho Tri-Cyclen® U.S. Package Insert). Ethinyl estradiol efficacy is expected to be maintained, and ethinyl estradiol continues to be considered a reliable and effective form of contraception in combination with fenebrutinib.

Preliminary data from Study GP39616 also suggest that fenebrutinib can be classified as a moderately sensitive substrate of CYP3A at clinically relevant doses. There is a moderate potential for a drug–drug interaction with any medication that strongly inhibits or induces this enzyme. Therefore, medications in the following categories should be avoided for 7 days or 5 drug-elimination half-lives, whichever is longer, prior to the first dose of fenebrutinib and during the treatment period (i.e., until the final dose of fenebrutinib):

- Strong CYP3A inhibitors
- Moderate or strong CYP3A inducers

4.4.2.4 Medications Given with Precaution due to Effects Related to Breast Cancer Resistance Protein

Preliminary data from Study GP39616 suggest that fenebrutinib is a moderate inhibitor of the breast cancer resistance protein (BCRP) (also known as ABCG2) at clinically relevant doses. Consequently, fenebrutinib may alter transport of BCRP substrates and result in increased plasma concentrations of BCRP substrates. Therefore, BCRP substrates with a narrow therapeutic window should be used with caution and in consultation with the Medical Monitor (or delegate) as needed:

4.4.2.5 Dose Adjustments for Statins due to Effects Related to Cytochrome P450 Enzymes or Breast Cancer Resistance Protein

Because several lipid-lowering agents (statins) are metabolized by CYP3A (simvastatin, lovastatin) and/or transported by BCRP (rosuvastatin, atorvastatin) and thus may be affected by drug–drug interaction with fenebrutinib, dose adjustments of these medications should be considered (Kellick et al. 2014), as outlined below:

- Simvastatin: recommended maximum dose of 10 mg/day
- Lovastatin: recommended maximum dose of 20 mg/day
- Rosuvastatin: recommended maximum dose of 10 mg/day
- Atorvastatin: recommended maximum dose of 20 mg/day

The use of statins has been associated with myopathy, which can manifest as weakness, tenderness, or muscle pain, with elevations of creatine kinase above 10 × upper limit of normal (ULN). In severe cases, myopathy can cause rhabdomyolysis with or without acute kidney injury secondary to myoglobinuria, and rare fatalities due to rhabdomyolysis have occurred. The risk of myopathy is increased by elevated plasma levels of statins. Predisposing factors for myopathy include advanced age (≥ 65 years), female sex, uncontrolled hypothyroidism, renal impairment, or use of concomitant medications that increase the plasma levels of the statin.

4.4.3 Prohibited Therapy

4.4.3.1 Live or Attenuated Vaccinations

Immunization with a live or attenuated vaccine is prohibited within 6 weeks prior to the first dose of fenebrutinib and during the treatment period.

Seasonal influenza vaccination is permitted if the inactivated vaccine formulation is administered.

4.4.4 Prohibited Food

Use of furanocoumarin derivatives, as found in grapefruit, Seville orange, pomegranate, or star fruit juice or products, is prohibited within 7 days prior to the first dose of fenebrutinib and during the treatment period (i.e., until the final dose of fenebrutinib).

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

All assessments on Day 1 are conducted prior to study drug administration unless otherwise specified. Assessments that were performed at the final visit of the parent study, if within 3 months prior to Day 1, should not be repeated.

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. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening (Day 1) evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment and receiving the first open-label dose in this study. 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 (including prior cancer therapies and procedures), and reproductive status, will be recorded at baseline in the parent study. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient from the time the patient completed the treatment period of the parent study will be recorded. Past resolved adverse events will be recorded in the medical history if clinically significant. Refer to Section 5.3.5.3 for information on recording adverse events that had not resolved at the end of the parent study. 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.

4.5.3 Physical Examinations

Limited, symptom-directed physical examinations should be performed at specified visits and as clinically indicated. Changes in parent study 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 measurement of pulse rate and systolic and diastolic blood pressure while the patient is in a seated position for at least 5 minutes.

4.5.5 Laboratory, [redacted] and Other Biological Samples

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis as per the schedule of activities:

- Hematology: hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent and absolute differential counts (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, other cells)
- Serum chemistry: bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, ALP, creatine phosphokinase, C-reactive protein, lipase, and uric acid
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- Coagulation: INR, aPTT, PT, and fibrinogen
- Lipid panel
- Plasma samples for PK analysis

The following laboratory tests will be sent to the site's local laboratory for analysis:

- Pregnancy test

  For women of childbearing potential: Urine pregnancy tests will be performed at specified visits. The patient will be requested to conduct monthly urine pregnancy tests at the site between in-clinic study visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[redacted]

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, biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma samples collected for PK analysis will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

[redacted]

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 will be subject to the confidentiality standards described in Section 8.4.

Given the complexity [redacted], 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.

4.5.6 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements.

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs can be performed without specific restrictions (e.g., can be performed at any time of day, before or after dosing, fasting or fed) but are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) 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 QT interval corrected through use of Fridericia's formula (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 postdose timepoint the mean QTcF is $>$500 ms 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. In such a scenario, 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 5.1.2.4. 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).

4.5.7 Patient-Reported and Clinician-Reported Outcomes

The Urticaria Patient Daily Diary and the Urticaria Control Test (UCT) will be collected to document the treatment benefit of fenebrutinib. The Physician's Global Assessment of Disease Control–Likert Scale (PhyGA-LS) will be collected to record the physician's assessment of disease control. The Urticaria Patient Daily Diary, UCT, and PhyGA-LS will be translated into the local language as required and will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, the UCT will be self-administered before the patient receives any information on disease status, prior to the performance of non–patient-reported outcome (non-PRO) assessments, and prior to the administration of study treatment, unless otherwise specified.

Patients will be instructed to complete a paper Urticaria Patient Daily Diary. The diary will be returned to the clinic, and the data will be sent for transcribing into the central database.

Patients will be given paper questionnaires to capture the UCT (see Appendix 3) at specified visits. Instructions for completing the questionnaires will be provided by the investigator staff. Paper forms will be transcribed into the central database.

4.5.7.1 Urticaria Patient Daily Diary

The Urticaria Patient Daily Diary includes questions regarding number of hives, largest hive size, sleep interference, activity interference, rescue medication use, angioedema episodes, and number of calls to the doctor, nurse, or nurse practitioner (see Appendix 2). Urticaria Activity Score (UAS) is derived from patient entries in the daily dairy and is used to calculate the UAS7 (see below).

The diary is to be completed by the patient twice daily (morning and evening) for the first 12 weeks of the study. The last diary entry may occur the day prior to the Week 12 visit.

Weekly Urticaria Activity Score

The UAS is a composite score with numeric severity intensity ratings (0=none to 3=intense/severe) for the number of wheals (hives) and the intensity of the pruritus (itch) over the past 12 hours as shown in Table 1 below. The UAS7 is sum of the average daily itch and hive score over 7 days and has a maximum value of 42.

Table 1 Twice-Daily Patient Assessment of CSU Disease Activity (UAS Scale)

Score	Wheals (Hives)	Pruritus (Itch)
0	None	None
1	Mild (1–6 hives/12 hour)	Mild
2	Moderate (7–12 hives/12 hour)	Moderate
3	Intense (>12 hives/12 hour)	Severe

4.5.7.2 The Urticaria Control Test

The UCT is a 4-item questionnaire to assess disease activity (see Appendix 3). The recall period is 4 weeks; the score range is 0–16 with a minimally important difference of 2.8 (Kulthanan et al. 2016). See Appendix 1 for UCT assessment timepoints.

4.5.7.3 Physician's Global Assessment of Disease Control–Likert Scale

The PhyGA-LS is a 5-point scale that reflects the investigator's assessment of the treatment over the previous 4 weeks. It has the following categories: no control, little control, moderate control, good control, and complete control (see Appendix 4).

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

Patients who discontinue study treatment either permanently or due to treatment interruption (see Section 5.1.2.2) will be asked to return to the clinic for a safety follow-up visit approximately 4 weeks after the last dose of study drug. Patients who refuse to complete the safety follow-up period should return to the clinic for a treatment discontinuation visit.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

4.6.2 Patient Discontinuation from 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 withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- 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 information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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 Sponsor must terminate the study if the Sponsor believes that the incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- The Sponsor may terminate the study if 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:

- The Sponsor must close a site if corrective actions to improve site performance in the following areas do not yield significant improvement:
  - 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., no patients remain in the OLE and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Fenebrutinib is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on nonclinical and clinical experience with fenebrutinib in completed and ongoing studies, as well as published literature on other BTK inhibitors and BTK biology. The anticipated important safety risks for fenebrutinib are outlined below. Please refer to the Fenebrutinib 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 monitoring of vital signs, ECGs, and routine laboratory safety assessments (hematology, chemistry, and urinalysis) and assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Potential Risks Associated with Fenebrutinib

5.1.1.1 Infections

Fenebrutinib is a reversible inhibitor of BTK, and the degree to which fenebrutinib antagonism of BTK signaling may suppress immune activity is unknown. On the basis of patients with X-linked agammaglobulinemia (XLA), a primary immunodeficiency caused by mutations in the *BTK* gene, it is anticipated that inhibitors of BTK may raise the risk for certain bacterial infections (Lederman and Winkelstein 1985; Broides et al. 2006), enteroviral infections (Misbah et al. 1992; Ziegner et al. 2002), intestinal infections with giardia and *Campylobacter* species (Winkelstein et al. 2006; van den Bruele et al. 2010), or other opportunistic infections, which are cleared primarily by B-cell adaptive immune responses.

Infections, including pneumonia, fatal influenza, nasopharyngitis, and asymptomatic bacteriuria, have occurred in patients treated with fenebrutinib.

The parent study protocol contains exclusion criteria for infections and potential infection risk, and patients with any clinically significant signs or symptoms of infection or infections requiring treatment with IV antibiotics since enrolling in the parent study will be excluded from the OLE study (see Section 4.1.2). All patients in the study should be monitored for fever and potential infectious complications, including opportunistic infections and tuberculosis, and should be evaluated promptly. Physicians or a health care provider should give patients advice to prevent potential transmission of and exposure to endemic infections according to local or Centers for Disease Control and Prevention guidelines. Patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of an infection.

All infections occurring during the study, including, but not limited to, respiratory infections, cutaneous infections, urinary tract infections, systemic viral infections, and episodes of suspicious or febrile diarrhea, should be evaluated using serology or polymerase chain reaction, if available, and cultured, if feasible, and any identified organisms noted in the eCRF. Any serious infection, infection requiring IV antimicrobials, or any opportunistic infection is considered an adverse event of special interest and should be reported to the Sponsor as outlined in Section 5.2.3.

Guidelines for management of patients who develop infections are provided in Table 2.

5.1.1.2 Vaccinations

The effect of fenebrutinib upon the efficacy of vaccinations is unknown. It is recommended that appropriate vaccinations per local guidelines be up to date before study participation. Patients will be excluded from study participation if they have been vaccinated with live, attenuated vaccines (e.g., the intranasal live attenuated influenza vaccines, bacille Calmette-Guérin, varicella) within 6 weeks prior to the first dose of study drug. Immunization with a live or attenuated vaccine is prohibited for the duration of study participation.

Household contact with children or others who have been vaccinated with live vaccine components may pose a risk to the patients receiving fenebrutinib. Following vaccination with live component vaccines, the virus may be shed in bodily fluids, including stool, and there is a potential risk that the virus may be transmitted to the patient. Thus, patients should avoid exposure to vaccinated individuals during defined periods for specified vaccines, as outlined below:

- Varicella or attenuated typhoid fever vaccination: 4 weeks following vaccination
- Oral polio vaccination: 6 weeks following vaccination
- Attenuated rotavirus vaccine: 10 days following vaccination
- FluMist® (inhaled flu vaccine): 1 week following vaccination

5.1.1.3 Bleeding

Bleeding events, including bruising and bleeding, have been reported in patients with hematological malignancies treated with fenebrutinib. The gastrointestinal (GI) bleeding events have not been dose related, and the events occurred in patients who were taking concomitant non-steroidal anti-inflammatory drugs and who had a history of gastroesophageal or peptic ulcer disease. The impact of BTK inhibition as a potential risk factor for bleeding is unknown. BTK is expressed in platelets and is involved in platelet function via glycoprotein VI collagen receptor signaling and glycoprotein Ib receptor signaling. Platelets from patients with XLA demonstrate decreased activation in response to submaximal collagen stimulation but normal response to thrombin; clinically, there is no reported bleeding propensity of patients with XLA.

Bruising or bleeding events related to fenebrutinib have not been reported in healthy subjects. Grade $\geq$2 bleeding events, including hematuria, purpura, hematoma, and uterine and vaginal bleeding, have been reported in blinded and open-label studies of fenebrutinib in autoimmune indications.

It is unknown whether fenebrutinib will increase the risk of bleeding in patients, especially in those receiving anti-platelet or anti-coagulant therapies. As a precautionary safety measure, the parent study protocol has exclusion criteria regarding anti-coagulant medications and other risk factors for serious bleeding events. Patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of clinically significant bleeding.

Bleeding events of moderate or greater severity are considered adverse events of special interest and should be reported to the Sponsor in an expedited manner as outlined in Section 5.2.3.

Guidelines for management of patients who experience bleeding events are provided in Table 2.

5.1.1.4 Cytopenias

Cytopenias, including neutropenia, anemia, and thrombocytopenia, have been observed in patients with hematological malignancies who received fenebrutinib. Events have been monitorable and clinically manageable.

Patients should be monitored with hematology laboratory evaluations as outlined in the schedule of activities (see Appendix 1) and should receive appropriate supportive care as clinically indicated. Patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of cytopenia (e.g., persistent fever, bruising, bleeding, pallor). Cytopenias should be managed according to local clinical guidelines.

5.1.1.5 Gastrointestinal Effects

Diarrhea, nausea, and abdominal pain have been reported in patients with B-cell malignancies; however, the events have resolved and have not led to study drug discontinuation. Healthy subjects in the multiple-ascending dose (MAD) Study GA29347 reported events of mild self-limited nausea.

Throughout the study, patients will be monitored for GI side effects.

Guidelines for management of patients who experience GI events are provided in Table 2.

5.1.1.6 Hepatotoxicity

In clinical studies to date in autoimmune indications enrolling over 800 patients, multiple cases of treatment emergent Grade 3 (severe) elevations of ALT, some of which were considered serious adverse events, have been observed. Cases have also been observed in blinded studies in CSU. None of the cases of transaminase elevations resulted in clinical jaundice or bilirubin $>2\times$ ULN (Hy's Law). All transaminase elevations have been reversible when dosing of study treatment was withheld. In addition, there have been no observed adverse events of liver enzyme elevation in clinical studies to date in healthy subjects or patients with hematological malignancies. To minimize this risk, patients with abnormal liver enzyme and function tests and current liver disease were excluded from the parent study.

Guidelines for the management of patients who develop ALT or AST elevations are provided in Table 2.

5.1.1.7 Cardiovascular Effects

Fenebrutinib is considered to have a low potential to cause QT interval prolongation or to directly affect other cardiovascular parameters at therapeutic exposures. Analysis of ECG data from the single-ascending dose and MAD studies in healthy subjects did not demonstrate any significant increase in either QRS interval or QTcF intervals. However, cardiac safety will be evaluated in all patients throughout this study, with routine

monitoring of vital signs (including pulse rate and blood pressure), and routine safety ECGs as outlined in the schedule of activities (see Appendix 1).

Guidelines for management of patients who experience cardiovascular events are provided in Table 2 and Section 5.1.2.4.

5.1.1.8 Vascular Inflammation

Drug-induced vasculitis typically involves the skin, but the lung and kidneys may be sites of involvement (Radić et al. 2012). Signs and symptoms associated with drug-induced vasculitis can be non-specific and include arthralgia, myalgia, fever, and rash (Banks and Freeman 2006; Sharma et al. 2011). All patients and subjects will be monitored during the study for adverse events suggestive of vasculitis as part of routine monitoring as outlined in the schedule of activities (see Appendix 1).

Guidelines for management of patients who develop vasculitis are provided in Table 2.

5.1.1.9 Malignancy

The impact of BTK inhibition on the development of malignancies is not known; however, malignancies have been identified as a potential concern for immunomodulatory agents. Malignancies have been reported in patients with XLA, including lymphoreticular malignancies, gastric and colorectal adenocarcinoma, and squamous cell carcinoma of the lung.

Patients with the history of cancer, including hematologic malignancy and solid tumors, were excluded in the parent study.

All malignancies are adverse events of special interest and should be reported to the Sponsor in an expedited manner as outlined in Section 5.2.3.

Guidelines for management patients who develop malignancies are provided in Table 2.

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

There will be no dose modifications for fenebrutinib in this study.

5.1.2.2 Treatment Interruption

Fenebrutinib treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug. If fenebrutinib has been withheld for >4 weeks because of toxicity, the patient should be discontinued from the study (see Section 4.6.1), unless resumption of treatment is approved following investigator discussion with the Medical Monitor. Fenebrutinib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.1.2.3 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 2. Additional guidelines are provided in the subsections below.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events

Event	Action to Be Taken [a]
Infection [b]	
Self-limited infections that require treatment	• Withhold fenebrutinib during antimicrobial therapy • Resume fenebrutinib after consultation with the Medical Monitor
Serious infection, opportunistic infection, or any infection requiring treatment with an IV antimicrobial agent	• Permanently discontinue fenebrutinib • Report event as an adverse event of special interest to Sponsor in an expedited manner
Bleeding	
Bleeding of moderate or greater severity	• Withhold fenebrutinib • Report event as an adverse event of special interest to Sponsor in an expedited manner • Resume fenebrutinib after consultation with the Medical Monitor
Serious bleeding or bleeding events requiring transfusion, radiologic endoscopic, or elective operative intervention	• Withhold fenebrutinib • Resume fenebrutinib after consultation with the Medical Monitor
Gastrointestinal events	
Nausea, vomiting, and/or diarrhea	• Continue fenebrutinib • Initiate symptomatic treatment and manage according to site institutional guidelines. • Consider administration of fenebrutinib with food as a possible mitigation strategy.
Malignancy	
Non-serious local and resectable basal or squamous cell carcinoma of the skin	• Continue fenebrutinib • Report event as an adverse event of special interest to Sponsor in an expedited manner
Other malignancy	• Permanently discontinue fenebrutinib • Report event as an adverse event of special interest to Sponsor in an expedited manner

QD = once a day; QTcF = QT interval corrected through use of Fridericia's formula; ULN = upper limit of normal.

[a] Any patient who permanently discontinues fenebrutinib should be followed for safety for 4 weeks after the last dose of fenebrutinib, if possible.

[b] Appropriate laboratory investigations, including, but not limited to, cultures should be performed to establish the etiology of any serious infection.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events (cont.)

Hepatotoxicity	
AST or ALT 3.0–5.0 × ULN	• Withhold fenebrutinib • Resume fenebrutinib after consultation with the Medical Monitor
AST or ALT > 3 × ULN in combination with a total bilirubin > 2 × ULN, of which at least 35% is direct bilirubin, or clinical jaundice	• Permanently discontinue fenebrutinib • Report event as an adverse event of special interest to Sponsor in an expedited manner
AST or ALT > 5 × ULN	• Permanently discontinue fenebrutinib • Report event as an adverse event of special interest to Sponsor in an expedited manner
Cardiovascular events (for additional information, see Section 5.1.2.4)	
Sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms or > 60 ms longer than the parent study baseline value	• Permanently discontinue fenebrutinib unless there is a clear alternative cause other than fenebrutinib [c]
Episode of torsades de pointes or new ECG finding of clinical concern	• Permanently discontinue fenebrutinib unless there is a clear alternative cause other than fenebrutinib [c]
Vascular inflammation Vasculitis	• Permanently discontinue fenebrutinib

QD = once a day; QTcF = QT interval corrected through use of Fridericia's formula; ULN = upper limit of normal.

[a] Any patient who permanently discontinues fenebrutinib should be followed for safety for 4 weeks after the last dose of fenebrutinib, if possible.

[b] Appropriate laboratory investigations, including, but not limited to, cultures should be performed to establish the etiology of any serious infection.

[c] In rare circumstances, it may be acceptable to resume fenebrutinib, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

5.1.2.4 Management of Increases in QT Interval

Patients who develop any of the following should have study drug discontinued unless a clear alternative cause other than fenebrutinib can be identified:

- Sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms or > 60 ms longer than the parent study baseline value
- 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. 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 any 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.

In rare circumstances, it may be acceptable to resume study drug, 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 Sections 5.3.5.8 and 5.3.5.9 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 5.3.5.10)
- 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; 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:

- Any serious infection, any infections requiring IV antimicrobials, and any opportunistic infections
- Bleeding events of moderate or greater severity
- Any malignancies
- Adverse events of special interest for general drug development

– Laboratory result of AST or ALT $>5\times$ ULN

– Cases of potential drug-induced liver injury that include an ALT or AST $>3\times$ ULN in combination with a total bilirubin $>2\times$ ULN (of which at least 35% is direct bilirubin) or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)

- 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 4 weeks 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

Table 3 provides guidance for assessing adverse event severity.

Table 3 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see 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 4):

- 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 4 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 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.

5.3.5.2 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 GI 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.

5.3.5.3 Persistent or Recurrent Adverse Events

Persistent Adverse Events First Reported in Study GS40868

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. 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.

Persistent Adverse Events First Reported in the Parent Study

An adverse event that is ongoing at the end of the parent study will be marked as not resolved in the eCRF for that study and will be reopened in this study with the same start date, adverse event term, and severity recorded in the parent study. The severity should be evaluated by the investigator at the start of this study and updated in the Adverse Event Intensity or Grade Changes eCRF if applicable.

Recurrent 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.

5.3.5.4 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

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., ALP 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) 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 $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value 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 5.3.5.1) 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).

5.3.5.7 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 CSU.

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 to angioedema or CSU, "angioedema" or "chronic spontaneous urticaria" 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.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening (Day 1) 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").

5.3.5.9 Lack of Efficacy or Worsening of Chronic Spontaneous Urticaria

Medical occurrences or symptoms of deterioration that are anticipated as part of CSU should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of CSU on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of chronic spontaneous urticaria").

5.3.5.10 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:

- Hospitalization for respite care
- 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

5.3.5.11 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.

5.4 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)
- Overdoses, medication errors, drug abuse, or drug misuse (see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events 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 Institutional Review Board or Ethics Committee (IRB/EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], M.D. (Primary)

Mobile Telephone No.: [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 4 weeks 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 >4 weeks 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 4 weeks 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 4 weeks 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. 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 when updated information on the course and outcome of the pregnancy 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 Congenital Anomalies/Birth Defects and Abortions

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). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.4.4 Reporting Requirements for Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (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
- Intentional overdose: intentional 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.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

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, 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 fenebrutinib, 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.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with fenebrutinib, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.

- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on 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.

5.5 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 4 weeks 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:

- Fenebrutinib 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

6.1 DETERMINATION OF SAMPLE SIZE

No formal sample size calculations were performed for this OLE study.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for study withdrawal 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, and self-reported race/ethnicity) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

6.4 SAFETY ANALYSES

The safety analysis population will consist of all patients who received at least one dose of study drug.

Safety will be assessed through descriptive summaries of adverse events and laboratory test results.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded.

6.5 EXPLORATORY EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all patients enrolled in this OLE study. Because of the non-comparative nature of the study, no statistical tests are planned. Efficacy parameters will be summarized descriptively. Details will be provided in the data analysis plan.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with at least one quantifiable plasma fenebrutinib concentration. Individual and mean plasma fenebrutinib concentration data will be tabulated and plotted by visit and/or dose level as applicable. Descriptive summary statistics will include the arithmetic mean, median, range, standard deviation, and coefficient of variation, as appropriate.

Additional PK analyses will be conducted as appropriate.

[redacted]

6.8 INTERIM ANALYSIS

No formal interim analysis is planned. Data cuts may be performed at appropriate timepoints for inclusion in the submission with the parent study to support evaluation of the safety profile.

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 and other additional non-eCRF data 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 and clinician-reported outcome (ClinRO) data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

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 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, PROs, ClinROs , 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 7.5.

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.

7.4 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO and ClinRO 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 Clinical Study Report has been completed 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 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. Food and Drug Administration 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).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form 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 [redacted], 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 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.

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.

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 Genentech and will be conducted globally. Data will be recorded via an EDC system from Medidata Solutions (New York, NY), using eCRFs (see Section 7.2). The contract research organization will be responsible for submission to IRB/ECs for approval of the study protocol, patient recruitment, data collection, and reporting.

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 of the U.S. National Institutes of Health and the European Medicines Agency, 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, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details). For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following web site:

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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Appendix 1
Schedule of Activities

	Study Site Visits [a] Year 1							Study Site Visits [a] Year 2–End of Study						
Week	1 [b]	4	8	12	24	36	52	12	24	36	52	UV	TD [c]	SC/ 4-Week SFU [d]
Day (Window)	1	28 (±7)	56 (±7)	84 (±7)	168 (±14)	252 (±14)	365 (±14)	84 (±14)	168 (±14)	252 (±14)	365 (±14)			(±14)
Informed consent	x													
Inclusion/exclusion criteria	x													
Concomitant medications [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [g]	x	x			x		x		x		x	(x)	x	x
Weight	x													
Limited physical examination [h]	x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
ECG [i]	x						x				x	(x)	x	x
Hematology [j]	x	x	x	x	x	x	x	x	x	x	x	(x)	x	x
Chemistry [k]	x	x	x	x	x	x	x	x	x	x	x	(x)	x	x
Lipid panel	x	x					x				x	(x)	x	x
Coagulation [l]	x						x				x	(x)		
Pregnancy test (urine) women [m]	x	Q4W										(x)	x	x
Urinalysis [n]	x	x					x				x	(x)	x	x
UCT [o]	x	x	x	x	x	x	x	x	x	x	x	(x)	x	x
PhyGA-LS [p]	x	x	x	x	x	x	x	x	x	x	x	(x)	x	x
Urticaria Patient Daily Diary [q]	x	x	x	x										
Plasma PK sample [r]	x			x	x		x		x		x	(x)	x	x
[redacted]														
Fenebrutinib administration [s]	x	BID												
Fenebrutinib dispensing [a]	x	Q4W												

Appendix 1: Schedule of Activities (Cont.)

BID = twice a day; CRP = C-reactive protein; CSU = chronic spontaneous urticaria; eCRF = electronic case report form; LDH = lactate dehydrogenase; OLE = open-label extension; PK = pharmacokinetics; PRO = patient-reported outcome; PhyGA-LS = Physician's Global Assessment of Disease Control-Likert Scale; Q4W = every 4 weeks; SC = study completion; SFU = safety follow-up; TD = treatment discontinuation; UAS = Urticaria Activity Score;UAS7 = Urticaria Activity Score over 7 days; UCT = Urticaria Control Test; UV = unscheduled visit.

Note: (x) = optional/as clinically indicated.

[a] Fenebrutinib tablets will be dispensed on site every 4 weeks. For periods in which study site visits (for assessments) are scheduled > 4 weeks apart, patients will be expected to visit site to receive allotment of study drug.

[b] All assessments on Day 1 are conducted prior to study drug administration unless otherwise specified. Activities that were performed at final visit of the parent study, if within 3 months prior to Day 1, should not be repeated.

[c] Patients who refuse to complete the safety follow-up period should return to the clinic for a treatment discontinuation visit.

[d] Patients who discontinue study treatment will be asked to return to the clinic for a safety follow-up visit approximately 4 weeks after the last dose of study drug (see Section 4.6.1).

[e] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from entry into the extension study to the final visit of the extension study. All such medications, including standard-of-care H_1-antihistamines for CSU, should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[f] 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. After initiation of study drug, all adverse events will be reported until 4 weeks after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[g] Includes measurement of pulse rate and systolic and diastolic blood pressure while the patient is in a seated position for at least 5 minutes

[h] Limited, symptom-directed physical examination should be performed on Day 1 and as clinically indicated. Changes in parent study baseline abnormalities should be recorded in patient notes. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] ECGs can be performed without specific restrictions (e.g., can be performed at any time of day, before or after dosing, fasting or fed) but are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

[j] Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent and absolute differential counts (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, other cells).

[k] Includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, ALP, creatine phosphokinase, CRP, lipase, and uric acid.

[l] Includes INR, aPTT, PT, and fibrinogen.

[m] For women of childbearing potential: urine pregnancy tests will be performed locally at specified visits. The patient will be requested to conduct monthly urine pregnancy tests at the site between in-clinic study visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (performed locally). .

[n] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[o] UCT to be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to study drug administration, unless otherwise specified.

[p] The PhyGA-LS reflects the investigator's assessment of the treatment over the previous 4 weeks. It has the following categories: no control, little control, moderate control, good control, and complete control (see Appendix 4).

[q] Patient is to complete the Urticaria Patient Daily Diary twice a day, approximately every 12 hours (morning/evening) through Week 12. The UAS is derived from patient entries in the daily dairy and is used to calculate the UAS7. The last diary entry may occur the day prior to the Week 12 visit.

[redacted]

[s] Patients will receive the first dose of fenebrutinib at the Day 1 study visit. Thereafter, fenebrutinib will be self-administered. Fenebrutinib may be taken with or without food. Patients should be instructed that a missed dose should not be taken with the next scheduled dose.

Appendix 2
Urticaria Patient Daily Diary

General Instructions

Please answer each question to the best of your ability.

There are no right or wrong answers.

For each question, please choose the response that describes your experience.

Please pay close attention to the timeframe of interest. Some questions ask about the **past 12 hours**, while others ask about the **past 24 hours**.

Instructions for Counting the Number of Hives and Measuring the Size of the Largest Hive

Count each hive separately even if you have more than one hive grouped together with other hives.

Please use the ruler that you have been given to measure the size of your largest hive. If you need help, please have someone else take this measurement for you. **Please do not measure a group of hives as one hive.**

Today's Date

		-				-				

Day **Month** **Year**

Please complete this section <u>every morning</u> throughout the duration of the study. (Please circle only one response.)

1. Thinking about the **<u>past 12 hours</u>**, please record the severity of itch and the number of hives you may have had associated with your skin condition. **<u>Please count each hive separately</u>** even if you have more than one hive grouped together with other hives.

Itch (severity)	Hives (number)
0 = none 1 = mild 2 = moderate 3 = severe	0 = none 1 = between 1 and 6 hives 2 = between 7 and 12 hives 3 = greater than 12 hives

This next question asks you to estimate the size of your largest hive in centimeters (cm). Please use the ruler that you have been provided to make this measurement. If your largest hive is located on your back or in a place that is hard to reach, please have someone else take this measurement for you. When measuring the largest hive size, **<u>please do not measure a group of hives as one hive.</u>**

Largest Hive (size)
0 = none 1 = less than 1.25 centimeter (cm) 2 = between 1.25 centimeter (cm) and 2.5 centimeters (cm) 3 = greater than 2.5 centimeters (cm)

Today's Date

		-				-				

Day **Month** **Year**

Please complete this section <u>every evening</u> throughout the duration of the study. (Please circle only one response.)

2. Thinking about the **<u>past 12 hours</u>**, please record the severity of itch and the number of hives you may have had associated with your skin condition. **<u>Please count each hive separately</u>** even if you have more one than one hive grouped together with other hives.

Itch (severity)	Hives (number)
0 = none 1 = mild 2 = moderate 3 = severe	0 = none 1 = between 1 and 6 hives 2 = between 7 and 12 hives 3 = greater than 12 hives

This next question asks you to estimate the size of your largest hive in centimeters (cm). Please use the ruler that you have been provided with to make this measurement. If your largest hive is located on your back or in a place that is hard to reach, please have someone else take this measurement for you. When measuring the largest hive size, **<u>please do not measure a group of hives as one hive.</u>**

Largest Hive (size)
0 = none 1 = less than 1.25 centimeter (cm) 2 = between 1.25 centimeter (cm) and 2.5 centimeters (cm) 3 = greater than 2.5 centimeters (cm)

Today's Date

		–				–				

Day **Month** **Year**

Please complete this section twice each day (a.m. and p.m.) throughout the duration of the study (preferably at the same time each day).

(Please circle only one response.)

3. Please rate how much your hives or itch interfered with your sleep during the **past 24 hours**.

   0 = No interference

   1 = Mild, little interference with sleep

   2 = Moderate, awoke occasionally, some interference with sleep

   3 = Substantial, woke up often, severe interference with sleep

4. Please rate how much your hives or itch interfered with your daily activities during **the past 24 hours**. This could include work, school, sports, hobbies, and activities with friends and family.

   0 = No interference

   1 = Mild, little interference with daily activities

   2 = Moderate, some interference with daily activities

   3 = Substantial, severe interference with daily activities

These next questions are about your symptoms and how you managed them during the past 24 hours.

5. During the **past 24 hours**, did you use loratadine or cetirizine in order to control symptoms of your skin condition such as itch or hives?

   0 = No

   1 = Yes

6a. During the **past 24 hours**, did you have any rapid swelling on your face, (especially your eyelids or lips), inside your mouth (including your throat or tongue), or elsewhere on your body? This rapid swelling, also called angioedema, is at a deeper level under your skin than hives.

   0 = No **(GO TO Question 7)** 1 = Yes

6b. If Yes, how did you treat this rapid swelling? **(Circle all that apply.)**

   0 = Did nothing (GO TO Question 7)

   1 = Took some prescription or non-prescription medication

   2 = Called my doctor, nurse or nurse practitioner

   3 = Went to see my doctor, nurse, or nurse practitioner

   4 = Went to the emergency room at the hospital

   5 = Was hospitalized

7. During the **past 24 hours**, did you or someone else call your doctor, nurse or nurse practitioner because of your skin condition?

   0 = No 1 = Yes

Appendix 3
Urticaria Control Test

Patient name:

Date: (dd mm yyyy):

Date of birth (dd mm yyyy):

Instructions: You have urticaria. The following questions should help us understand your current health situation. Please read through each question carefully and choose an answer from the five options that *best fits* your situation. Please limit yourself to *the last 4 weeks. Please do not think about the questions for a long time*, and do remember to answer *all questions* and to provide *only one answer to each question.*

1. How much have you suffered from the **physical symptoms of the urticaria (itch, hives (welts) and/or swelling)** in the last 4 weeks?

   O very much O much O somewhat O a little O not at all

2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?

   O very much O much O somewhat O a little O not at all

3. How often was the **treatment** for your urticaria in the last 4 weeks **not enough** to control your urticaria symptoms?

   O very often O often O sometimes O seldom O not at all

4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?

   O not at all O a little O somewhat O well O very well

Appendix 4
Physician's Global Assessment of Disease Control–Likert Scale (PhyGA-LS)

How would you rate the control of the patient's symptoms within the previous 4 weeks?

□ no control

□ little control

□ moderate control

□ good control

□ complete control

Appendix 5
Cautionary Therapy: Concomitant Medications (Including Foods and Herbal Products) with Specific Drug-Drug Interaction

Class	Expected Interaction	Recommendation	Examples of Drugs in this Class [a]
Antacids	Decreased fenebrutinib absorption due to increased gastric pH	Take fenebrutinib 2 hours before or 2 hours after antacid	• Pepto-Bismol®, Rolaids®
Strong CYP3A inhibitors	Increased fenebrutinib plasma concentrations due to inhibition of metabolism	Avoid for 7 days or 5 drug-elimination half-lives (whichever is longer) prior to first dose of fenebrutinib and during the treatment period (i.e., until the final dose of fenebrutinib)	• Antimicrobials (clarithromycin, erythromycin, itraconazole, ketoconazole, telithromycin, troleandomycin, voriconazole, posaconazole) • Antidepressants (nefazodone) • Antihypertensive/cardiac (verapamil, diltiazem) • Other (grapefruit juice, Seville orange juice, pomegranate, star fruit)
Moderate or strong CYP3A inducers	Decreased fenebrutinib plasma concentrations due to increased metabolism	Avoid for 7 days or 5 drug-elimination half-lives (whichever is longer) prior to first dose of fenebrutinib and during the treatment period (i.e., until the final dose of fenebrutinib)	• Antimicrobials (rifampin, rifapentine, rifabutin) • Antidepressants (St. John's wort, hyperforin) • Antiepileptics (carbamazepine, phenytoin, phenobarbital, hyperforin) • Diabetes (pioglitazone, troglitazone) • Other (modafinil, bosentan)

[a] Note that the medications listed below are not necessarily comprehensive. Consult the prescribing information and refer to the following websites for additional information:

- U.S. Food and Drug Administration Table of Substrates, Inhibitors, and Inducers (Tables 3-1, 3-2, 3-3, and 5-1): (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)
- Indiana University Department of Medicine P450 Interaction Table: (http://medicine.iupui.edu/clinpharm/ddis/clinical-table)

Class	Expected Interaction	Recommendation	Examples of Drugs in this Class [a]
Sensitive and narrow therapeutic window CYP3A substrates	Potential for increased plasma concentrations of CYP3A substrates due to inhibition of metabolism by fenebrutinib	Use with caution and monitor for adverse events related to CYP3A substrates as directed by product labeling; consult with the Medical Monitor as needed	• Antiemetic/prokinetic (aprepitant, cisapride) • Antihistamine (astemizole, terfenadine) • Antihypertensive/cardiac (dronedarone, eplerenone, felodipine, nisoldipine, quinidine, ticagrelor, vardenafil) • Benzodiazepines (alprazolam, diazepam, midazolam) • Lipid-lowering (simvastatin [recommended maximum dose: 10 mg/day], lovastatin [recommended maximum dose: 20 mg/day]) • Migraine (eletriptan, ergotamine) • Steroids (budesonide, fluticasone) • Other (alfentanil, buspirone, conivaptan, darifenacin, dasatinib, dihydroergotamine, fentanyl, lurasidone, pimozide, quetiapine, sildenafil, tolvaptan, triazolam)
BCRP substrates with a narrow therapeutic index	Potential for increased plasma concentrations of BCRP substrates due to inhibition of transport by fenebrutinib	Use with caution and monitor for adverse events related to BCRP substrates as directed by product labeling; consult with the Medical Monitor as needed	• Antihypertensive (prazosin) • Anti-inflammatory (sulfasalazine) • Lipid-lowering (rosuvastatin [recommended maximum dose: 10 mg/day], atorvastatin [recommended maximum dose: 20 mg/day] • Muscle relaxants (dantrolene) • Steroids (estrone-3-sulfate)

[a] Note that the medications listed below are not necessarily comprehensive. Consult the prescribing information and refer to the following websites for additional information:

- U.S. Food and Drug Administration Table of Substrates, Inhibitors, and Inducers (Tables 3-1, 3-2, 3-3, and 5-1): (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm)
- Indiana University Department of Medicine P450 Interaction Table: (http://medicine.iupui.edu/clinpharm/ddis/clinical-table)

Appendix 6
Fenebrutinib Bottle and Label Configuration

Label to be affixed on the study drug bottle displays morning (sun) and evening (moon) doses.

Site will be responsible for prepopulating the dates on the label and affixing the label to the bottle.

Patients should record on the label the time in military (24-hour) time of each dose taken.