PROTOCOL

Study Title: **Preventing Life-Threatening Allergic Reactions with Ibrutinib, an FDA-Approved BTK Inhibitor**

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Study Drug: Ibrutinib (Brand name: Imbruvica®)

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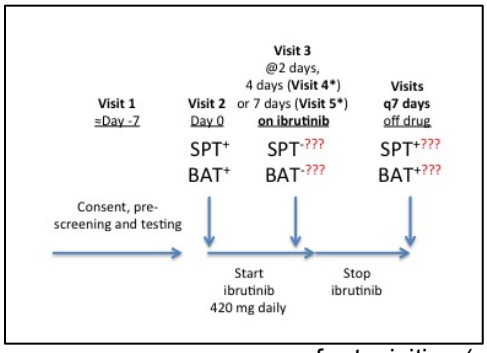
LIST OF ABBREVIATIONS

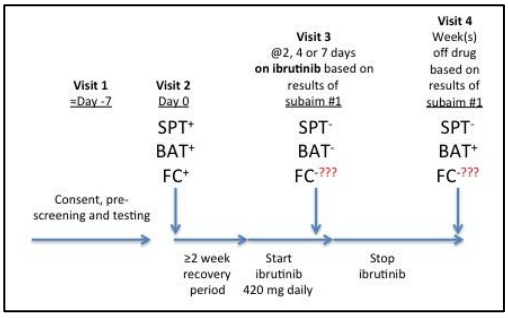
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BAT	Basophil Activation Test
BTK	Bruton's Tyrosine Kinase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CLL	Chronic Lymphocytic Leukemia
CMP	Comprehensive Metabolic Panel
CRU	Clinical Research Unit
SBPC	Single-blind Placebo-controlled
DLT	Dose-Limiting Toxicity
DSMB	Data and Safety Monitoring Board
EKG	Electrocardiogram
FC	Food Challenge
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IgE	Immunoglobulin E
IV (or iv)	Intravenously
MCL	Mantle Cell Lymphoma
MTD	Maximum Tolerated Dose
OFC	Oral Food Challenge
PBMCs	Peripheral Blood Mononuclear Cells
p.o.	per os/by mouth/orally
PST	Peripheral Blood Testing
SAE	Serious Adverse Event
sIgE	Surface Immunoglobulin E
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
SPT	Skin Prick Test
WBC	White Blood Cells
WM	Waldenstrom's Macroglobulineia

This is a phase II open label study on the use of Ibrutinib on the inhibition of food-induced anaphylaxis in adults with food allergy. Ibrutinib (brand name Imbruvica) is currently FDA approved for the treatment of mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and Waldenstrom's macroglobulineia (WM). We propose to administer this approved drug to adults with food allergy to inhibit anaphylaxis.

STUDY SCHEMA

This is open-label study consists of 2 parts. Part 1 is designed to determine the fewest doses and shortest length of time, from two days to up to 7 days, needed for ibrutinib to fully inhibit tests for food allergy, and to determine the length of persistence of efficacy after the drug is stopped. Part 2 is designed to determine the ability of ibrutinib, optimally dosed as defined in Part 1, to prevent signs and symptoms of anaphylaxis during a food challenge in food-allergic subjects.





Clinical protocol for part 1 (top) and part 2 (bottom). + or - = predicted response; ??? **=** question to be answered; *** =** if needed

Part 1: At **Visit 1**, after undergoing informed consent subjects will be screened for eligibility (history, skin prick test [SPT] to peanut/tree nuts with histamine and saline SPT positive and negative controls, respectively, basophil activation test [BAT], peanut or tree nut-specific IgE). 30 mL of peripheral blood will be collected by a trained phlebotomist using standard procedures for BAT, sIgE to peanut/tree nuts and components, quantitative immunoglobulins (QUIGs), eosinophil and basophil enumeration, as well as screening for toxicities (see below). After this visit, subjects will be given ibrutinib (two doses of 420 mg of ibrutinib to start the following day and to be taken orally at 8am exactly 24 hours apart) and return for **Visit 2** to undergo repeat PST and phlebotomy for testing preformed in an identical manner to Visit 1. If two consecutive doses of 420 mg of ibrutinib given 24 hours apart is insufficient to cause >80% inhibition of the SPT and BAT response, subjects will be given two additional doses of 420 mg of ibrutinib to continue to take at 8am exactly 24 hours apart for two more days, and return for **Visit 3** for identical repeat testing as in Visits 1 and 2**.** If four consecutive doses of 420 mg of ibrutinib given 24 hours apart is insufficient to cause >80% inhibition of the SPT and BAT response, subjects will be given three additional doses of 420 mg of ibrutinib to continue to take 24 hours apart for three more days, and return for **Visit 4** for identical repeat testing as in Visits 1, 2 and 3, where based on preliminary data, we expect SPT and BAT to be suppressed. Once both the SPT and BAT responses are inhibited, no further ibrutinib doses will be given, and subjects will return on a weekly basis until both the peanut/tree nut PST and BAT return to at least 80% of baseline values. At this point, Part 1 will have been completed. At each visit, patients will be monitored for toxicities, including CBC, CMP, and pregnancy testing. Prior to drug initiation and at the end of the trial, an EKG will be performed.

Part 2: Visit 1 will be identical to those for Part 1 except that subjects will take a higher dose of ibrutinib (560mg daily) for 2 days and a single-blind, placebo-controlled (SBPC) graded food challenge of up to 8 mg of peanut or tree nut protein, administered over escalating doses, will be performed in a monitored at the study site in a clinical research unit (CRU) setting. Prior to the SBPC food challenge, 30 mL of peripheral blood will be collected for BAT, sIgE to peanut and components, as well as for total IgE, eosinophil and basophil enumeration. During the challenge, subjects will be repeatedly assessed for signs and symptoms of food-induced anaphylaxis between each dose per food challenge protocol. This visit will establish each subject's baseline threshold dose for peanut/tree nut reactivity.

Once a confirmed reaction occurs, the food challenge will be terminated and the reaction treated until it has resolved. Within 15 minutes of a positive challenge, an additional 10 mL of blood will be drawn for mast cell microparticle analysis. After a minimum of a two week recovery period, each subject will then begin taking ibrutinib 560 mg orally daily for 2 days, which is the minimum number of doses that

demonstrate efficacy as determined in Part 1. Two hours after the final dose, subjects will return to the study site for **Visit 2,** and PST and SBPC food challenges will be repeated to establish each subject's new threshold dose for peanut/tree nut reactivity while on ibrutinib, and with repeat post-challenge blood collection for mast cell microparticle analysis. At this point of the protocol, ibrutinib dosing will be stopped. Follow up visits starting 3 months after cessation of ibrutinib will be conducted to repeat toxicity labs and skin testing.

STUDY SUMMARY

Title	Inhibition of Anaphylaxis by Ibrutinib
Protocol Number	BB20150924
Phase	Phase 2
Methodology	Open label study to determine dosing and safety of Ibrutinib for the treatment of food allergy
Study Duration	12 weeks
Study Center(s)	Single-center
Objectives	Primary: To determine the shortest amount of time and fewest ibrutinib doses required to eliminate food SPT and BAT reactivity and to evaluate the effect of pretreatment with ibrutinib on food allergen reactivity in food allergic subjects given ibrutinib 420 mg daily for 2-7 doses Secondary: To determine if a suppressed SPT response to peanut, despite normal BAT responses, predicts whether a SBPC food challenge will be altered from baseline threshold dose for peanut reactivity.
Number of Subjects	12
Diagnosis and Main Inclusion Criteria	Adults with food-challenge proven food allergy to peanut (or tree nut)will be invited to participate.
Study Product(s), Dose, Route, Regimen	Ibrutinib 420 or 560 mg, PO once daily
Duration of administration	2-7 days
Reference therapy	There are currently no approved therapies for food allergy
Statistical Methodology	Descriptive statistics will be used to determine 80% reduction in allergy test size (skin testing) and basophil degranulation during treatment.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Food allergy is a potentially life threatening disease, and its prevalence continues to increase despite public health efforts (1,2) Newer studies have shown that it is less likely that a subject will lose their food allergies over time and food allergies can also start in adulthood, so more adults now have life-threatening food allergies. Near fatal and fatal reactions can occur of subjects with food allergies and can lead to devastating results (3,4). Furthermore, the economic burden of childhood food allergy is nearly $25 billion per year, including 200,000 emergency department trips annually (5). Despite this significant disease burden, there are currently no approved therapies for food allergy. Standard of care is constant vigilance in avoidance of allergen, and use of self-injected epinephrine after a reaction has occurred. Therefore, there is a large unmet need for new therapeutics to prevent serious allergic disease including food allergy and anaphylaxis. Newly FDA approved BTK inhibitors such as ibrutinib (as well as others under development (6,7)) may be able to fill this void, and offer a therapy to these subjects.

1.2 Study Drug Background and Associated Known Toxicities

Ibrutinib is a once daily, oral, selective, irreversible small-molecule inhibitor of Bruton's tyrosine kinase (BTK), a key component of B-cell receptor signaling (8,9). BTK is also essential for FcεRI signaling and triggering of mast cells and basophils (10){Iyer, 2011 #10272;Kuehn, 2008 #10273;MacGlashan, 2011 #8797}. It is currently FDA approved for the treatment of Mantle Cell Lymphoma (MCL), Chronic Lymphocytic Leukemia (CLL) and Waldenstrom's macroglobulinemia (WM).

In subjects with recurrent B-cell lymphoma, >90% irreversible occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of >/= 2.5 mg/kg/day. Ibrutinib is absorbed with a median Tmax of 1-2 hours. It is metabolized by cytochrome P450 and CYP3A, and has a half-life of 4-6 hours. The majority (80%) is fecally excreted.

The approved CLL and WM dose (420 mg orally once daily) has been shown to inhibit allergy test responses in cancer subjects receiving this drug by 1 week of treatment (the earliest time point examined) in preliminary data from our group. The 560 mg dose (used for MCL) has similar side-effect and toxicity profiles as the lower dose. Initial data from Part 1 suggests that the 420mg dose can at least partially (in some cases fully) inhibit skin test responses to peanut and tree nuts in allergic subjects after just 2 doses, with minimal side effects and no observed toxicity thus far in subjects taking ibrutinib for up to 7 days. Therefore, we can justify using the higher dose of 560 mg orally once daily for Part 2 to investigate whether this higher dose can further reduce skin test responses beyond what is seen with the lower dose.

In human studies, ibrutinib is metabolized in the liver, and not significantly renally cleared. In healthy volunteers, co-administration with CYP3A inhibitors increased Cmax, and therefore the drug will not be concomitantly administered with strong or moderate inhibitors of CYP3A. Known toxicities in cancer subjects receiving ibrutinib chronically include bleeding events (5% of MCL subjects), infection (25% of MCL subjects), myelosuppression (41% of subjects), and renal toxicity has also been reported. Ibrutinib is also pregnancy category D. This underscores our goal of finding the fewest possible doses to achieve the anti-allergy effect we are seeking, which could be as few as just 2 doses.

1.3 Rationale

There are currently no treatments for food allergy. IgE uniquely arms mast cells and basophils via their surface expression of FcεRI in allergy. Crosslinking of the receptor is known to activate a number of SRC-family kinases (e.g., LYN, SYK) required for receptor function. BTK is a key

component of FcεRI signaling and triggering of mast cells and basophils. Since signaling mediated by FcεRI aggregation is thought to require the activity of BTK (8,9), MacGlashan et. al. (9) tested ibrutinib, formerly known as PCI-32765, for its ability to prevent activation of human basophils *in vitro.* For stimulation with anti-IgE, ibrutinib inhibited CD63, CD203c and CD11b upregulation, and release of histamine, LTC4 and IL-4 as well as the cytosolic calcium response (IC_{90} of ≈50 nM). Ibrutinib did not inhibit basophil activation by FMLP or C5a and did not inhibit IL-13 release induced by IL-3, suggesting that BTK is required for IgE-mediated activation of human basophils. We propose to test whether this pharmacology can be exploited *in vivo* to prevent allergic reactions.

Peanut and tree nut allergies are among the most common adult food allergens, and can often be the most severe. Additionally, peanut and tree nut allergies are often life-long. Young adults and adolescents have a higher rate of accidental exposure and mortality as a result of food allergies than younger children, so there is an unmet need for therapies directed at food allergy, especially in this population. Therefore, we have chosen peanut and tree nut allergies in an effort to investigate a treatment that has the potential to benefit the most individuals with a potentially severe allergy.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To determine if short term administration of ibrutinib to adults with peanut (or tree nut) allergy will safely change allergen challenge thresholds

2.2 Secondary Objectives

2.2.1 To describe the adverse events associated with ibrutinib when administered in a short course of 2-7 doses daily

2.2.2 To determine the minimum number of doses of ibrutinib needed to inhibit testing for food allergy (SPT and BAT)

2.2.3 To determine the length of effect of inhibition of testing for food allergy after the drug is stopped (SPT and BAT)

2.2.4 To determine if 2-7 daily doses of ibrutinib have any impact on blood levels of total and food-specific IgE, and numbers of circulating eosinophils and basophils.

2.3 Endpoints

Primary Objective 2.1.1: The highest dose of food allergen that is tolerated in a food challenge prior to reaction occurring in a food challenge, both before and while taking ibrutinib.

Secondary Objective 2.2.1: Adverse events, including bleeding, hepatotoxicity and renal toxicity will be monitored.

Secondary Objective 2.2.3: Change in SPT size and percent activation of basophils from BAT will be determined.

Secondary Objective 2.2.4: Change in blood levels of total and food-specific IgE, and numbers of circulating eosinophils and basophils.

Exploratory Objective: Clinical signs and symptom of food allergy reactions will be compared among subjects at oral food challenge visit in the study.

3.0 SUBJECT ELIGIBILITY

Subjects must meet all of the inclusion and exclusion criteria to be enrolled in the study. Study procedures may not begin until a subject signs the informed consent form.

3.1 Inclusion Criteria

3.1.1 History of food allergy to peanut (or tree nut).

3.1.2 Male or female age ≥ 18 years.

3.1.3 Positive skin prick testing and basophil activation test to the trigger food(s), either peanut and/or tree nut(s).

3.1.4 Clinical reaction to oral food challenge at baseline (for Part 2 only)

3.1.5 Adequate organ and marrow function as defined below:

- leukocytes	≥ 3,000/mcL
- absolute neutrophil count	≥ 1,500/mcL
- platelets	≥ 100,000/mcl
- total bilirubin	within normal institutional limits
- AST(SGOT)/ALT(SPGT)	within normal institutional limits
- Creatinine	within normal institutional limits

3.1.6 Women of child bearing potential must agree to two forms of highly effective contraception (hormonal, device, or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform the Principal Investigator and her treating physician immediately.

3.1.5.1 A female of child bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.7 Ability to understand and the willingness to sign a written informed consent.

3.1.8 Ability to clearly understand and speak English at an 8th grade reading level. For safety reasons, subjects must speak English due to the anticipated need for clear and timely communication with investigators and the study team in emergency situations, since the investigators and study team are English speaking.

3.2 Exclusion Criteria

3.2.1 Subjects who have been on immunomodulatory therapies or oral corticosteroids within 1 month prior to study participation will be excluded, and those taking antihistamines must stop these drugs for one week prior to enrollment and must refrain from taking antihistamines during the duration of the study so as not to interfere with SPT responses.

3.2.2 Subjects with symptoms not consistent with type 1 food reactions (atopic dermatitis, eosinophilic esophagitis and any other non-IgE-mediated food sensitivities) will be excluded.

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ibrutinib.

3.2.4 Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, beta-blocker use or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.5 Subjects must not be pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.

3.2.6 Subjects on anticoagulants, anti-platelet therapy, or any other predisposition towards bleeding.

3.2.7 Subjects with history of idiopathic urticaria, dermatographism, idiopathic or unexplained anaphylaxis, or anaphylaxis (to foods or otherwise) resulting in intubation, prolonged hypotension, or neurological sequelae

3.3 Study Stopping Criteria

The study will be stopped if >50% of patients cannot complete the protocol due to toxicities or adverse events. Toxicities (section 4.2) and adverse events (section 7.0) are listed below. Monitoring is described in section 8.0.

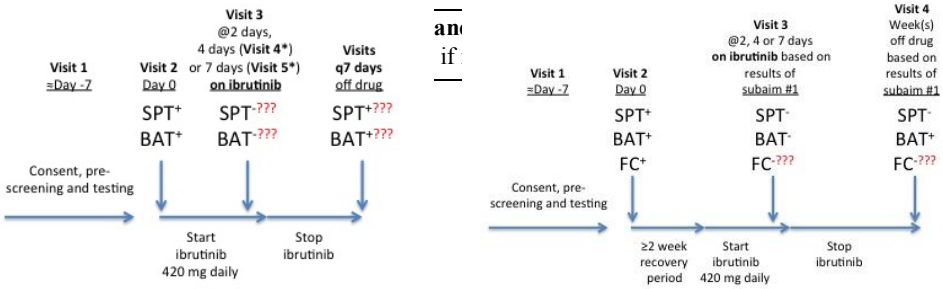
3.4 Recruitment

Patients with a diagnosis of peanut or tree nut allergy by a board certified allergist-immunologist will be identified as potential subjects from the allergy clinics at Northwestern University Feinberg School of Medicine. The treating physician will ask potential subjects permission to be contacted by study personnel. Potential subjects will then be contacted by authorized study personnel and given time to review the study information and consider participation.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

For Part 1 of the study, we will determine the length of treatment (i.e., the number of daily doses) required to inhibit both basophil and food skin test responses. Preliminary data demonstrates that 7 days of treatment will inhibit both basophil and mast cell responsiveness to aeroallergens, but have not yet tested shorter time points. Prior studies in cancer subjects suggest that one dose is sufficient to completely inhibit BAT, but we propose a minimum of two doses to allow for diffusion and penetration of ibrutinib into the skin compartment where our SPT is performed to assess skin mast cell responsiveness. For Part 1, 6 subjects will take ibrutinib 420 mg, by mouth once daily (every 24 hours) on an outpatient basis. After two days, the subject will undergo blood testing and SPT to assess basophil and mast cell reactivity. If both tests are negative, Part 1 is completed. If both tests are not negative, then the subject will take 2 more days of ibrutinib (same dose, for a total of 4 doses), and identical testing will be repeated. If testing is not negative at day 4, the subject will take 3 more days of ibrutinib (same dose, for a total of 7 doses), which is the maximum anticipated number of doses needed to suppress both the BAT and SPT.



For Part 2 of the study, 6 subjects will take ibrutinib 560 mg once daily by mouth (every 24 hours) for 2 days, which is the minimum number of days required to cause ≥80% inhibition of food SPT and BAT responses as determined in part 1. Part 2 will last a minimum of 3 days.

Dose-limiting toxicity (DLT) includes any grade 3 or 4 hematologic toxicity, grade 3 hepatotoxicity or increase in creatinine x 2.5 normal limit. DLT will be monitored at each visit, at any time during treatment.

Maximally tolerated dose (MTD) will occur at the point DLT occurs. Ibrutinib is approved as a daily medication for another indication, and we propose to use the drug in adults only at its approved oral dosing of 420 or 560 mg daily for a minimum of two days and a maximum of 7 days. Dose limiting events include grade 3 or 4 hematologic events, grade 3 or 4 hepatotoxicity, AST or ALT >3 times normal range, creatinine > 2.5 times normal range. DLT evaluation will be completed throughout the study, anytime during treatment.

In healthy volunteers, co-administration with CYP3A inhibitors increased C_{max}, and therefore the drug will not be concomitantly administered with strong or moderate inhibitors of CYP3A (for example, “azole” medications and subjects will be advised against drinking grapefruit juice).

4.2 Toxicities and Dosing Delays

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each subject will be assessed for the development of toxicity according to the Time and Events table (Section 5.4).

At each visit, subjects will be monitored for toxicities. If a subject develops a grade 3 or 4 hematologic, renal, or hepatotoxicity, the medication will be stopped. Toxicities with grades are listed below.

Hematological Toxicities:

Hematological Toxicity Dose Reductions for Ibrutinib		
ANC	**Platelets**	**Action**
≥ 1,500/μL	100,000/μL	None.
1000-1499/μL	75,000-99,000/μL	*-1st Occurrence:* Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose. *-2nd Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses.

		-3rd Occurrence: Discontinue protocol therapy.
500-999/μL	50,000-74,000/μL	*-1st Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose. *-2nd Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Do not replace missed doses. Restart next treatment at TBD dose. *-3rd Occurrence*: Discontinue protocol therapy.
<500/μL	<50,000/μL	*-1st Occurrence*: Hold current dose until ANC ≥ 1,500/μL and platelets ≥ 100,000/μL. Restart next treatment at TBD dose. *-2nd Occurrence*: Discontinue protocol therapy.

Renal Toxicity: Creatinine will be monitored per protocol. Creatinine levels >2.5 times the normal limit will result in discontinuation of protocol therapy.

Hepatotoxicity: Grade 3 hepatotoxicity, or an increase in AST or ALT >3 times upper limit of normal will result in discontinuation in protocol therapy.

4.3 Concomitant Medications/Treatments

The following concomitant medications/treatments are not allowed: immunomodulatory therapies, oral corticosteroids within 1 month of study participation; those taking antihistamines must stop these drugs for one week prior to enrollment and must refrain from taking antihistamines during the duration of the study so as not to interfere with SPT responses; and any other prior investigational interventions.

4.4 Duration of Therapy

Treatment will continue for a minimum of 2 days and a maximum of 7 days per Part 1 of the protocol. Other reasons the medication may be discontinued include:

- Inter-current illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Subject decides to withdraw from the study; or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.5 Duration of Follow Up

Subjects will be followed until SPT and BAT return to baseline in Part 1, and for up to 6 months after cessation of ibrutinib treatment in Part 2. Subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. The Principal Investigator will be notified. The reason for study removal and the date the subject was removed will be documented in the Case Report Form. The subject will be followed-up per protocol.

4.6 Subject Replacement

Subjects who withdraw voluntarily from the study, but were tolerating the drug will be replaced. Subjects who drop out or miss doses due to toxicity will not be replaced since these subjects will be considered to have experienced a dose limiting toxicity.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining written informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 14 days prior to start of treatment. The screening procedures include:

5.1.1 **Informed Consent**

Informed consent will be obtained per IRB and GCP guidelines.

5.1.2 **Medical history**

Complete medical and surgical history, history of infections will be obtained.

5.1.3 **Demographics**

Age, gender, race, ethnicity will be obtained.

5.1.4 **Review subject eligibility criteria**

Subjects will be screened to ensure they meet inclusion and exclusion criteria, including history and prior laboratory testing consistent with a diagnosis of IgE mediated food allergy.

5.1.5 **Review previous and concomitant medications**

Medications will be reviewed and documented.

5.1.6 **Physical exam including vital signs, height and weight**

Vital signs (temperature, pulse, respirations, blood pressure), height, weight and basic full physical exam will be performed by study physicians.

5.1.7 **Adverse event assessment**

Baseline adverse events will be assessed. This will include a CMP and CBC, EKG. See section 6 for Adverse Event monitoring and reporting.

5.1.8 **Hematology**

Baseline CBC will be performed.

5.1.9 **Blood draw for correlative studies**

See Section 9.0 for details.

5.1.10 **Serum chemistries**

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.11 **Pregnancy test (for females of child bearing potential)**

See section 3.1.6.1 for definition.

5.1.12 **Immunoglobulin levels**

Total quantitative immunoglobulins (QUIGs), including IgG, IgA, IgM, and IgE, as well as serum specific IgE for peanut/tree nuts will be monitored

5.1.13 **Spirometry**

To be performed before SBFC if the patient has a history of asthma or exercise-induced bronchospasm.

5.2 Procedures During Treatment (Part 1)

5.2.1 **Screening visit (Day 0) (Screening visit testing will be completed before drug administration)**

Screening:

- Physical exam, vital signs
- CBC
- CMP
- Immunoglobulin levels
- EKG
- Urine Pregnancy test (if required)

Procedures (to be done only if labs and EKG are within normal limits):

- Skin-prick testing
- Basophil activation test

5.2.2 **Day 2 (or 4 or 7 depending on when skin testing and basophil activation test return to baseline)**

- Skin prick testing
- Basophil activation test
- Hematology
- Serum chemistries
- Immunoglobulin levels

5.2.3 **After treatment termination (Termination and End of Study visits; time point determined when both skin prick testing and basophil activation testing return to baseline)**

- Physical exam, vital signs
- Hematology
- Serum chemistries
- Immunoglobulin levels
- EKG
- Urine Pregnancy test (if required)

5.3 Procedures During Treatment (Part 2)

5.3.1 Screening/Baseline visit (Visit 1)

Screening:

- Physical exam, vital signs
- Urine Pregnancy test (if required)
- CBC
- CMP
- Immunoglobulin levels
- EKG
- Spirometry (only if the subject has a history of asthma)

Procedures (to be done only if labs and EKG are within normal limits)

- Skin prick testing
- Basophil activation test
- SBPC oral food challenge as follows:

All oral food challenges (OFC) shall be performed as single (patient)-blinded, placebo controlled food challenges according to standard published guidelines (11, 12). Placebo challenge and active challenge will be performed in that order on the same day if the subject has no symptoms during the first (placebo) challenge. If a reaction requiring treatment occurs during the first challenge, the next challenge should not be performed until the symptoms have subsided. Oral food challenge to peanut or tree nut protein will be performed according to standard operating procedure. At physician discretion, based upon history and possible subjective or very mild objective symptoms during a challenge, dosing intervals may be extended.

Actions to minimize risk of severe allergic reactions during oral food challenge (OFC):
Prior to the OFC visit, subjects will be told to contact study staff about asthma and seasonal allergy symptoms, fever, acute infections including upper respiratory infections, rashes or change in status of chronic medical conditions. OFCs will be rescheduled in the event that any of these occur. Study staff will contact subjects 1-3 days before the OFC to inquire about recent symptoms.

All OFCs will be conducted in the Clinical Research Unit within the main hospital. Intravenous access will be obtained before the OFC begins. Emergency medications (epinephrine, diphenhydramine, cetirizine, albuterol, ranitidine) will be immediately accessible in the subject's room. All OFCs will be conducted by trained personnel and supervised by a clinician with experience in performing OFCs and trained in the treatment of anaphylaxis. Spirometry (assessment of pulmonary function) will be performed prior to the onset of the OFC. Vital signs and pulse oximetry will be obtained at baseline and prior to each dose of the food allergen and q15 minutes thereafter with an observation period of at last 2 hours after the last dose is consumed (longer should a reaction occur). The OFC will begin with a low dose, which will increase incrementally. At physician discretion, based upon history and possible subjective or very mild objective symptoms during a challenge, dosing intervals may be extended. The procedure will be stopped when clear objective symptoms are noted.

Subjects will be discharged after a period of observation appropriate to the nature of the symptoms. They will receive information regarding possible delayed manifestations and home treatment. All subjects will be provided with an epinephrine auto-injector to take home (if they do not have one already) and instructions on how and when to use it.

5.3.2 **Visit 2**

- Skin prick testing
- Basophil activation test
- CBC
- CMP
- Immunoglobulin levels
- Spirometry (only if the patient has a history of asthma)

- SBPC oral food challenge as follows:

All oral food challenges (OFC) shall be performed as single(patient)-blind, placebo controlled food challenges according to standard published guidelines (11, 12). Placebo challenge and active challenge will be performed in that order on the same day if the subject has no symptoms during the first (placebo) challenge. If a reaction requiring treatment occurs during the first challenge, the next challenge should not be performed until the symptoms have subsided. Oral food challenge to peanut or tree nut protein will be performed according to standard operating procedure.
At physician discretion, based upon history and possible subjective or very mild objective symptoms during a challenge, dosing intervals may be extended.

Actions to minimize risk of severe allergic reactions during oral food challenge (OFC):
Prior to the OFC visit, subjects will be told to contact study staff about asthma and seasonal allergy symptoms, fever, acute infections including upper respiratory infections, rashes or change in status of chronic medical conditions. OFCs will be rescheduled in the event that any of these occur. Study staff will contact subjects 1-3 days before the OFC to inquire about recent symptoms.

All OFCs will be conducted in the Clinical Research Unit within the main hospital. Intravenous access will be obtained before the OFC begins. Emergency medications (epinephrine, diphenhydramine, cetirizine, albuterol, ranitidine) will be immediately accessible in the subject's room. All OFCs will be conducted by trained personnel and supervised by a clinician with experience in performing OFCs and trained in the treatment of anaphylaxis. Spirometry (assessment of pulmonary function) will be performed prior to the onset of the OFC. Vital signs and pulse oximetry will be obtained at baseline and prior to each dose of the food allergen and q15 minutes thereafter with an observation period of at last 2 hours after the last dose is consumed (longer should a reaction occur). The OFC will begin with a low dose, which will increase incrementally. At physician discretion, based upon history and possible subjective or very mild objective symptoms during a challenge, dosing intervals may be extended. The procedure will be stopped when clear objective symptoms are noted.

Subjects will be discharged after a period of observation appropriate to the nature of the symptoms. They will receive information regarding possible delayed manifestations and home treatment. All subjects will be provided with an epinephrine auto-injector to take home (if they do not have one already) and instructions on how and when to use it.

5.4 Follow-up Procedures

Subjects will be followed every month after completion of (or early withdrawal from) study treatment until testing returns to baseline. Toxicity monitoring will be repeated (including hematology, serum chemistries, QUIGs, ssIgE) at 3 months after cessation of ibrutinib; if at this time they are not yet back to baseline, they will be repeated at 6 months.

- Physical exam, vital signs
- Urine Pregnancy test (if required)
- CBC
- CMP

- Immunoglobulin levels
- Skin prick testing

5.5 Time and Events Table

5.4.1. Part 1

Visit	1	2	3[a]	4/Early Termination	End-of-Study
	Screening / Day 0	Day 2	Day 4 or Day 7	Every 7 days until all allergy testing returns to baseline positive	Final Visit when all allergy testing is positive
Informed Consent	X				
Skin prick testing	X	X	X	X	
Basophil activation test	X	X	X	X	
History and PE	X				X
Toxicity (include DLT) Evaluations	X	X	X	X	X
CBC	X	X	X	X	X
CMP	X	X	X	X	X
EKG	X				X
Urine pregnancy testing[b]	X	X	X	X	X

[a] If required
[b] Females of child-bearing potential only

5.4.2. Part 2

Visit	1	2	3
	Screeing / Day 0	Day 2	Follow up (3 and/or 6 months after Visit 2)
Informed Consent	X		
Skin prick testing	X	X	X
Basophil activation test	X	X	
SBPC food challenge	X	X	
History and PE	X	X	X

Toxicity (include DLT) Evaluations	X	X	X
CBC	X	X	X
CMP	X	X	X
EKG	X	X	
Urine pregnancy test[b]	X		

[b] Females of child-bearing potential only

5.6 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements;

5.5.4 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.5.5 Treating physician judges continuation on the study would not be in the subject's best interest;

5.5.6 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event); or

5.5.7 Lost to follow-up. If a research subject cannot be located after a period of 2 months, the subject may be considered "lost to follow-up." All attempts to contact the subject during the 2 months must be documented.

6.0 RESPONSE CRITERIA

6.1 Safety/tolerability

Analyses will be performed for all subjects having received at least one dose of study drug. CBC, CMP, EKG will be performed on all subjects to monitor for toxicities and safety.

6.2 Efficacy

Increase in quantity of food that can be ingested on oral food challenge, decreased skin prick tests and decreased basophil activation will be used to assess efficacy of the treatment.

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

For the most recent safety update, please refer to the current Study Agent Prescribing Information. (This drug is currently FDA approved for alternate indications. Sections below are from the current package insert).

7.1.1 Contraindications

None.

7.1.2 Special Warnings and Precautions for Use

Prior studies of ibrutinib adverse events were performed on cancer patients who had often failed other treatments, and were treated chronically. However, Advani et. al. (13) reported side effects in a phase 1 study for only 28 days, the shortest duration of treatment that has been reported in the literature. In that study, a total of 56 patients with a variety of relapsed B-cell malignancies were treated over seven dosage cohorts (1.25 - 12 mg/kg/day). For the cohort receiving dosages closest to the one being used in our study (a total of 6 subjects given 5 mg/kg/day, or 420 mg/day for an 81 kg person) the most common adverse events were typically grade 1 or 2 in severity. Grade 3 or 4 events were infrequent and independent of dose. Data from this cohort of 6 subjects was extracted and reproduced from Table 3 of the Advani et. al. paper below. For the entire cohort of 56 subjects, Grade 3-4 hematologic toxicities included neutropenia (12.5%), thrombocytopenia (7.2%) and anemia (7.1%). According to the authors, no evidence of cumulative hematologic or non-hematologic toxicity was observed in patients with prolonged dosing, nor was any consistent relationship seen between dose level and adverse events.

	Diarr-hea	Nausea vomiting	Consti-pation	Decreased appetite dyspepsia	Fatigue	Insomnia	Head ache	Muscle spasms myalgia	Other pain	Pyrexia	Rash	Cough	Other respiratory	Arthral-gia	Edema
Grade 1-2	1	3	2	1	0	1	1	2	5	2	0	3	3	2	1
Grade 3-4	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0

As the subjects enrolled in this study will be generally healthy except for food allergy, and on ibrutinib for a much shorter duration (maximum of 7 days, perhaps as little as 2 days), we expected adverse events to be milder and less frequent, if at all, compared to prior studies of ibrutinib in cancer trials. However, for completeness, adverse events as documented with chronic use are detailed below.

7.1.2.1 Hemorrhage

Five percent of patients with MCL had Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, and hematuria). Overall, bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily.

The mechanism for the bleeding events is not well understood.

7.1.2.2 Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of patients with MCL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events CTCAE) (14).

7.1.2.3 Myelosuppression

Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients. These included neutropenia (29%), thrombocytopenia (17%) and anemia (9%). Monitor complete blood counts monthly.

7.1.2.4 Renal Toxicity

Fatal and serious cases of renal failure have occurred with ibrutinib therapy. Treatment- emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients and from 1.5 to 3 times the upper limit of normal in 9% of patients. Periodically monitor creatinine levels. Maintain hydration.

7.1.2.5 Embryo-Fetal Toxicity

Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Ibrutinib caused malformations in rats at exposures 14 times those reported in patients with MCL receiving the ibrutinib dose of 560 mg per day. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking ibrutinib. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

7.1.3 Interaction with other medications

As stated, metabolism of ibrutinib is inhibited by CYP3A inhibitors. Patients on these medications will be excluded.

7.1.4 Adverse Reactions

As per package insert (15), adverse reactions are listed in Section 7.1.2. Of note, patients in the trial references took a larger dose and for much longer duration that we propose in this study.

The most commonly occurring adverse reactions (approx. 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite.

The most common Grade 3 or 4 non-hematological adverse reactions (approx. 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of approx. 10%.

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mcL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

8.0 ADVERSE EVENT MONITORING

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study drug/device, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event

return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

8.1 Definitions

8.1.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

8.1.2 Severity of Adverse Events

The severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the subject unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the subject was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

8.1.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

8.1.3.1 Results in death.
If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

8.1.3.2 Is life-threatening.
(the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

8.1.3.3 Requires in-subject hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

8.1.3.4 Results in persistent or significant disability or incapacity.

8.1.3.5 Is a congenital anomaly/birth defect.

8.1.3.6 Is an important medical event.

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the subject, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event". For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

8.2 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event.

Step 2: Grade the adverse event.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

8.3 Reporting Requirements for Adverse Events

8.3.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- The Northwestern University IRB must be notified within 5 business days of any unanticipated problems involving risk to subjects or others (UPIRSO).

  The following events meet the definition of UPIRSO:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.
7. The FDA should be notified within 7 business days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and 15 business days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

8.3.2 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.3.3 Stopping Rules

The study will be stopped if >50% of patients cannot complete the protocol due to toxicities or adverse events.

9.0 DRUG INFORMATION

9.1 Ibrutinib 140 mg tablets

- Other names for the drug(s)/device: Imbruvica®
- Classification - type of agent/device: small molecule BTK inhibitor

Mode of action: Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

- Storage and stability: Ibrutinib is stored at room temperature and the tablets are stable.
- Protocol dose: 420 or 560 mg once daily for 2-7 days
- Preparation: as supplied from the manufacturer
- Route of administration for this study: By mouth
- Incompatibilities: N/A

- Availability: commercially available by prescription. Medication will be paid for through NIH funding, and provided free of charge to subjects.
- Side effects: Most common side effects are diarrhea, nausea, fatigue and musculoskeletal pain. Other side effects include myelosuppression, bleeding and hepatoxicity. Please refer to package insert for comprehensive list of side effects.
- Nursing implications: Ibrutinib is category D. It should not be used in nursing mothers.

9.2 Return and Retention of Study Drug

Study drug will obtained by the research pharmacy at Northwestern Feinberg School of Medicine by prescription only. Study drug will dispensed as needed, until next follow up. Therefore, we do not anticipate retention of study drug. However, if there is unused study drug, it will be disposed of in an appropriate manner.

9.2.1 Compliance will be assessed by subject diary and self-report.

10.0 STATISTICAL CONSIDERATIONS

Descriptive statistics will be completed to determine an 80% reduction in skin prick wheal size and basophil activation test reactivity (as determined by % inhibition of anti-IgE-induced CD63 expression). As this is an open label study, each patient's responsiveness will be examined compared to themselves prior to initiation of treatment.

10.1 Study Design/Study Endpoints

This is an open label study of ibrutnib in 12 food allergic adults to determine the shortest amount of time and fewest ibrutinib doses required to eliminate food SPT and BAT reactivity and to evaluate the effect of pretreatment with ibrutinib on food allergen reactivity in food allergic subjects given ibrutinib 420 or 560 mg daily for 2-7 doses. Given the nature of the study, it will be stopped if >50% of patients have a DLT at target enrollment.

10.2 Sample Size and Accrual

12 subjects allows 80% power to detect a reduction in skin test positivity rate from 100% before treatment to 15% after treatment using a one-sided 0.05 level McNemar's test. Patients will be recruited from the allergy clinics at Northwestern University Feinberg School of Medicine with a diagnosis of peanut (or tree nut) allergy by a board certified allergist-immunologist.

10.3 Data Analyses Plans

As this is an open label trial, descriptive statistics will be used. Each patient will be compared to him/herself prior to beginning treatment and at each time point in the study to assess SPT size (parts 1 and 2), BAT response (parts 1 and 2), and OFC threshold and response (part 2).

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by Northwestern Feinberg School of Medicine. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.3 Data Management and Monitoring/Auditing

As has been done previously for the phase 1 study of ibrutinib (13), adverse events will be monitored throughout treatment and toxicities will be assessed using the National Cancer Institute Common Toxicity Criteria for AEs, with its latest version, currently version 4.03.

11.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.4.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

11.4.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.

- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within two (2) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

11.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the subject, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.6 Confidentiality

The specimens will be coded and data will be stored in the Allergy-Immunology Research Labs, Mezzanine, McGaw Pavilion, or in locked file cabinets and/or on password protected computers. Only the study personnel will have access to the specimens and data generated. The PI and the study team members will be responsible for receipt or transmission of the data and specimens. The specimens will be maintained until exhausted or until the study ends. If there are remaining samples at the end of the study, any identifying information will be removed from the sample vial and the specimens will be treated with 10% bleach and discarded. Unused portions of the specimens may be shared with other members of the University community. The original data will remain with the PI in the Allergy Division. No PHI will be shared.

11.7 Provisions to Protect the Privacy Interests of Subjects

Certain other people besides the PI and his research team may review the results of the study, such as administrative staff members from the Office of Research, Office of Research Integrity and members of the Institutional Review Board, and members of the Office for Human Research Protections. There is a slight risk that a subject's privacy might be at risk. All of the above mentioned people in the respective capacities are obligated to protect a subject's privacy and have training and certification in the safeguarding of the patient's privacy. All data and results will be maintained in the Allergy-Immunology Research Labs, Mezzanine, McGaw Pavilion, in locked file cabinets and/or on password protected computers.

To help the subjects feel at ease, these safeguards are outlined in the consent form.

As far as information in medical records, only licensed medical personnel would have permission to access the information.

11.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDIX 1: Pill Diary

MONTH _____

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

The study coordinator will fill in the month and days.
Please document number of pills and time you took the ibrutinib.